Determinants of plasma platelet-activating factor acetylhydrolase: heritability and relationship to plasma lipoproteins

Rudy Guerra,[††] Biren Zhao,[*] Vincent Mooser,[†] Diana Stafforini,[§§] John M. Johnston,[*] and Jonathan C. Cohen[1,§,]**

Departments of Biochemistry,[*] Molecular Genetics,[†] and Internal Medicine,[§] and the Center for Human Nutrition,[**] UT Southwestern Medical Center, Dallas, TX 75235; Department of Statistical Science,[††] Southern Methodist University, Dallas, TX 75275; and the Program in Human Molecular Biology,[§§] Eccles Institute of Genetics, University of Utah, Salt Lake City, UT

Abstract Plasma platelet-activating factor acetylhydrolase (PAF-AH) is the enzyme that inactivates PAF (1-alkyl-2-acetyl-*sn*-glycero-3-phosphocholine). We determined the relative contributions of genetic and environmental factors to variation in plasma PAF-AH activity in 240 individuals from 60 nuclear families. Regression of mean-offspring PAF-AH activity on the mid-parent value indicated that 62% of the variation in plasma PAF-AH activity was heritable. Spousal values were weakly negatively correlated, indicating that familial aggregation of PAF-AH activity is due to genetic rather than to environmental factors. Among normolipidemic individuals, plasma PAF-AH activity was strongly correlated with the plasma concentration of low density lipoprotein cholesterol (LDL-C), and treatment with lovastatin resulted in proportional decreases in plasma PAF-AH activity and LDL-C concentrations. To further elucidate the relationship between PAF-AH and plasma concentrations of LDL, plasma PAF-AH activity was measured in families with well-defined, monogenic disorders of LDL metabolism. Plasma PAF-AH activity cosegregated with plasma LDL-C concentrations in familial hypercholesterolemia, but not in familial hypobetalipoproteinemia. We speculate that the rate of removal of LDL from the circulation may determine the clearance rate of PAF-AH, thereby modulating the activity of PAF-AH in blood.—**Guerra, R., B. Zhao, V. Mooser, D. Stafforini, J. M. Johnston, and J. C. Cohen.** Determinants of plasma platelet activating factor acetylhydrolase: heritability and relationship to plasma lipoproteins. *J. Lipid Res.* 1997. **38:** 2281–2288.

Supplementary key words low density lipoprotein • familial hypercholesterolemia • lovastatin • familial hypobetalipoproteinemia

Platelet-activating factor (PAF) is a naturally occurring ether phospholipid that mediates diverse biological processes (1, 2). In most systems, full biological activity of PAF is achieved at very low concentrations (10^{-11} M), and the rates of PAF synthesis and degradation are rigorously controlled (1). PAF entering the circulation is rapidly inactivated to lyso-PAF by PAF acetylhydrolase (PAF-AH), a phospholipase A_2 with a marked preference for phospholipids with a short chain fatty acid moiety at the *sn*-2 position (3). The plasma form of PAF-AH appears to be secreted largely by macrophages. PAF-AH from human plasma has been extensively characterized, and the activity of the enzyme in plasma has been found to be altered in several pathological conditions. However, the causes of inter-individual variation in PAF-AH activity have not been fully elucidated. Several factors have been shown to affect the secretion of PAF-AH from macrophages in vitro (4–8), but much less is known about the determinants of plasma PAF-AH activity in vivo. In the circulation, PAF-AH is transported in plasma lipoproteins (9–11), predominantly low density lipoproteins (LDL), and plasma PAF-AH activity is strongly correlated with plasma LDL cholesterol (LDL-C) concentrations (12). These studies indicate that variation in plasma LDL-C concentrations accounts for about one-third of the inter-individual variation in plasma PAF-AH activity. Furthermore, plasma PAF-AH activity is normal in patients with abetalipoproteinemia (13–15), a genetic condition in which apolipoprotein B-containing lipoproteins including LDL are absent from the circulation. In these individuals, plasma PAF-AH activity is associated with the high density lipoprotein (HDL) fraction (13, 14). This finding indicates that LDL are not required for plasma PAF-AH activity.

Abbreviations: PAF-AH, plasma platelet-activating factor acetylhydrolase; LDL-C, low density lipoprotein cholesterol; DFP, difluorophosphate.

[1]To whom correspondence should be addressed.

Among healthy individuals, plasma PAF-AH activity may vary over a 5-fold range, but the activity of the enzyme within a given individual remains relatively constant over time (J. M. Johnston, unpublished data). Variation in plasma PAF-AH activity may therefore be heritable. A mutation that abolishes the activity of the enzyme is very common in the Japanese population (16, 17), but the relative contributions of genetic and environmental factors to variation in plasma PAF-AH activity have not been determined in other populations. To determine the heritability of plasma PAF-AH activity, we have examined its segregation in normolipidemic families. Our data indicate that genetic factors account for approximately 60% of the inter-individual variation in plasma PAF-AH activity. Plasma PAF-AH activity and LDL-C levels were strongly correlated, but a significant fraction of the heritable variation in plasma PAF-AH activity was independent of plasma LDL-C levels. To further elucidate the relationship between this enzyme and plasma concentrations of LDL, plasma PAF-AH activity was measured in families with well-defined, monogenic disorders of LDL metabolism.

METHODS

Subjects

The procedures used in this study were approved by the Institutional Review Board of the University of Texas Southwestern Medical Center at Dallas. Blood was collected from 240 individuals in 60 nuclear families, each of which comprised two parents and their two oldest offspring. None of these individuals had monogenic dyslipidemia and none used lipid-lowering drugs or hormone replacement therapy. To investigate the effects of dyslipidemia on plasma PAF-AH activity, 7 additional families were collected. Three families with hypercholesterolemia were obtained based on the presence of plasma LDL-C concentrations greater than the 95th percentile, and tendon xanthomas. The hypercholesterolemia was shown to be secondary to familial hypercholesterolemia by documenting cosegregation of the hypercholesterolemia with a single LDL receptor allele. None of the individuals in these families used lipid-lowering drugs. Two families with hypobetalipoproteinemia that cosegregated with a single apolipoprotein B allele were obtained. The apolipoprotein B mutation in one of these families (C to A at apoB cDNA nucleotide 11458) has been the subject of a previous report (18). Two families were ascertained through patients with severe hypertriglyceridemia. Both of these patients had fasting plasma triglyceride concentrations in excess of 1000 mg/dl.

Lovastatin treatment

Twenty individuals ingested 40 mg lovastatin per day for 8 weeks. Blood samples were drawn before commencing the drug phase and after 8 weeks of treatment. In two additional subjects, 40 mg lovastatin was given for 12 days. Blood samples were drawn before and on days 0, 1, 2, 3, 4, 5, 8, 10, and 12, and 3 days after cessation of treatment.

Assay of plasma lipoproteins

Plasma concentrations of cholesterol and triglyceride were assayed in duplicate using standard enzymatic methods. High density lipoprotein cholesterol was determined by sodium phosphotungstate precipitation as described previously. Low density lipoprotein cholesterol concentrations were calculated using Friedewald's formula. The correlation between plasma LDL-C and plasma apolipoprotein B (the major protein of LDL) was 0.88.

Assay of plasma PAF-AH

The activity of this enzyme was assayed in duplicate according to the method of Miwa et al. (17), with minor modifications (8). This method determines [^{3}H]acetate release from [^{3}H]PAF as catalyzed by plasma PAF-AH. Plasma was diluted 10-fold with 0.25 M sucrose. The assay mixture contained 50 μl of diluted plasma, Tris-HCl (30 mM, pH 7.5) and 25 nmol of 1-hexadecyl-2-[^{3}H]acetyl-*sn*-glycero-3-phosphocholine (New England Nuclear, Boston, MA) in fatty acid-free bovine serum albumin (0.13% final concentration), in a total volume of 0.5 ml. The incubation time was 20 min at 37°C. The reaction was terminated by the addition of trichloroacetic acid (14%) and centrifuged. One-tenth of 1 ml of supernatant was added to 5 ml of scintillation fluid (Budget-Solve, Mt. Prospect, IL) and the release of [^{3}H]acetate was determined by liquid spectroscopy (Packard Instrument Co. Downers Grove, IL). The activity of PAF-AH was expressed as nanomoles acetate released per minute per ml of plasma (nmol · min^{-1} · ml^{-1}).

Effect of exogenous LDL on PAF-AH

The effect of exogenous LDL was tested by treating plasma or purified LDL with diflurophosphate (DFP) to inactivate PAF-AH, dialyzing excess inhibitor, and then adding increasing amounts of the treated plasma or LDL to a fixed volume of native plasma in the PAF-AH assay mixture. Volumes of DFP-treated plasma or LDL were adjusted so as to increase the LDL concentration in the assay mix by 1-, 2-, and 5-fold.

Statistical analysis

Statistical computing was performed on a Sun Sparcstation using Splus.

The distribution of plasma PAF-AH activity was tested for normality using the Kolmogorov-Smirnov test.

Correlations between PAF-AH activity and covariates including age, and plasma lipoprotein concentrations were estimated using Pearson's correlation.

An unpaired *t*-test was used to compare PAF-AH activity between men and women. A paired *t*-test was used to compare PAF-AH activity before and after lovastatin treatment.

PAF-AH values were adjusted for variation in plasma LDL-C by linear regression.

The heritability index of plasma PAF-AH activity was estimated by regressing the average of the offspring plasma PAF-AH values on the mid-parent values using weighted least squares. Weights to adjust for unequal family sizes were calculated as suggested by Falconer (19), with an unweighted least squares estimate used as the initial estimate of heritability in the weights.

RESULTS

The observed plasma PAF-AH activities were skewed with a long right tail and differed significantly from a normal distribution ($P = 0.008$). Log-transformed PAF-AH values did not significantly differ from a normal distribution ($P = 0.08$).

Influence of age, sex, and plasma lipoproteins on PAF-AH activity

Among individuals who did not have monogenic dyslipidemia, plasma PAF-AH activity was significantly correlated with age and with plasma concentrations of triglyceride, HDL-C, and LDL-C (**Table 1**). Similar correlations were observed using observed and log-transformed PAF-AH data (Table 1). PAF-AH activity was lower in women than in men (35 ± 11 vs. 44 ± 11 nmol $\cdot$ min^{-1} $\cdot$ ml^{-1}, $P < 0.001$). A clear linear relationship was apparent between plasma PAF-AH activity and LDL-C concentration (**Fig. 1**). There was considerable variation around the least squares regression line, however, and variation in plasma LDL-C accounted for only 36% of the variation in plasma PAF-AH activity. Pearson correlations were also performed after adjusting the observed PAF-AH activities for the effects of LDL-C. Adjustment for LDL-C almost completely abolished the correlation between PAF-AH activity and age but had little effect on the correlations observed between plasma PAF-AH activity and triglyceride and HDL-C concentrations (Table 1).

TABLE 1. Correlations between plasma PAF-AH activity, age, and plasma lipid and lipoprotein concentrations[a]

	Log PAF-AH	PAF-AH	RPAF-AH[b]
Age	0.36	0.34	0.05
Cholesterol	0.57	0.56	0.03
Triglyceride	0.33	0.31	0.31
HDL-C	−0.27	−0.30	−0.32
LDL-C	0.61	0.60	0.00
Apo-B	0.71	0.72	0.23

[a]n = 260; $P < 0.05$ for $|r| > 0.10$.
[b]RPAF-AH denotes residual PAF-AH values after adjustment for LDL-C by linear regression.

Heritability of PAF-AH activity

Data from 60 nuclear families were used to estimate the heritability of plasma PAF-AH activity. Regression of mean offspring PAF-AH activity on the midparent value indicated that heritable factors accounted for 62% of the variation in plasma PAF-AH activity (**Fig. 2**). Heritability on the log-scale was estimated to be 72%. Similar results were obtained after adjustment for sex (not shown). Regression adjustment of the PAF-AH activity to exclude the effects of variation in LDL-C did not significantly affect the heritability estimate on either the observed (H = 0.59) or log (H = 0.75) scale. PAF-AH activity was not significantly correlated between spouses ($r = -0.19$, $P = 0.14$).

PAF-AH activity in monogenic dyslipidemia

Plasma PAF-AH activity cosegregated with plasma LDL-C concentrations in all three families with familial hypercholesterolemia (**Fig. 3**). Individuals heterozygous for a mutant LDL-R allele had plasma PAF-AH activities that were 2- to 3-fold higher than those of their unaffected siblings. In contrast, PAF-AH activity did not co-segregate with LDL-C in familial hypobetalipoproteinemia, despite 3-fold differences in plasma LDL-C among affected and unaffected siblings (**Fig. 4**). Plasma PAF-AH activity was similar in hypertriglyceridemic and normotriglyericemic siblings, despite 10-fold differences in plasma triglyceride levels (**Fig. 5**).

Effects of exogenous LDL on PAF-AH activity

To determine whether LDL directly affected the activity of PAF-AH in our assays, we tested added exogenous LDL (previously inactivated with DFP to abolish endogenous PAF-AH activity) to a source of enzyme (native plasma). Addition of DFP-treated plasma or purified LDL to the PAF-AH assay did not significantly influence the PAF-AH activity measured in a test sample over a 5-fold range of LDL-C concentrations.

Effects of lovastatin on plasma LDL-C concentration and PAF-AH activity

Plasma LDL-C concentrations and PAF-AH activities were significantly decreased after lovastatin treatment

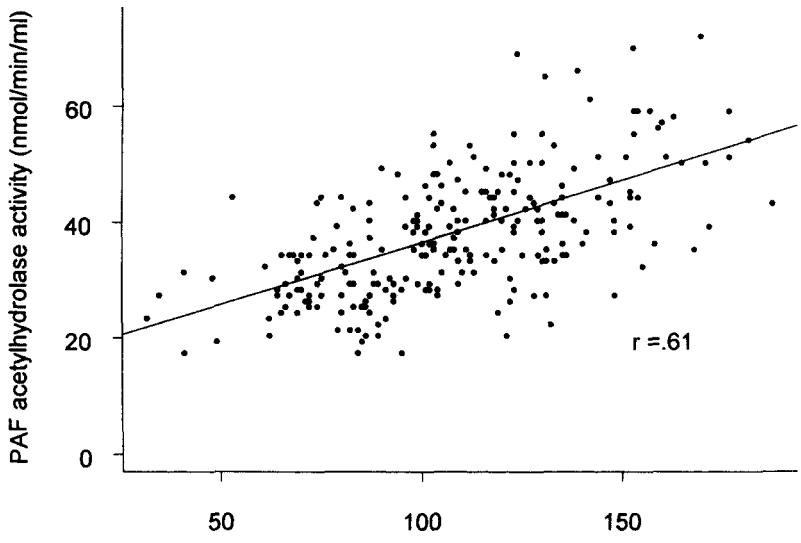

Fig. 1. Scatterplot of plasma PAF-AH activity and LDL-C concentration.

($P < 0.0001$, paired t-test). The magnitude of the decrease in PAF-AH activity correlated with the decrease in LDL-C concentration (**Fig. 6**). In two subjects from whom blood samples were taken during the first 2 weeks of treatment, the decrease in PAF-AH activity closely paralleled the decrease in plasma LDL-C concentrations (data not shown).

DISCUSSION

Plasma PAF-AH activity varies over a wide range among healthy, normolipidemic individuals. In this study we show that inter-individual variation in plasma PAF-AH activity arises from both genetic and nongenetic factors. By comparing the observed plasma PAF-AH activities of parents with those of their children we determined that 60% of the total variation in plasma PAF-AH activity is heritable. As nearly all of the offspring in this study lived with their parents, this heritability estimate may be confounded by shared environmental factors. The correlation between spousal plasma PAF-AH activities was weakly negative and did not achieve statistical significance, suggesting that shared environmental factors do not contribute appreciably to familial aggregation of this trait. Thus the familial aggregation of PAF-AH activity appears to be due to common genes rather than to a shared environment.

The specific genes that confer heritable variation in

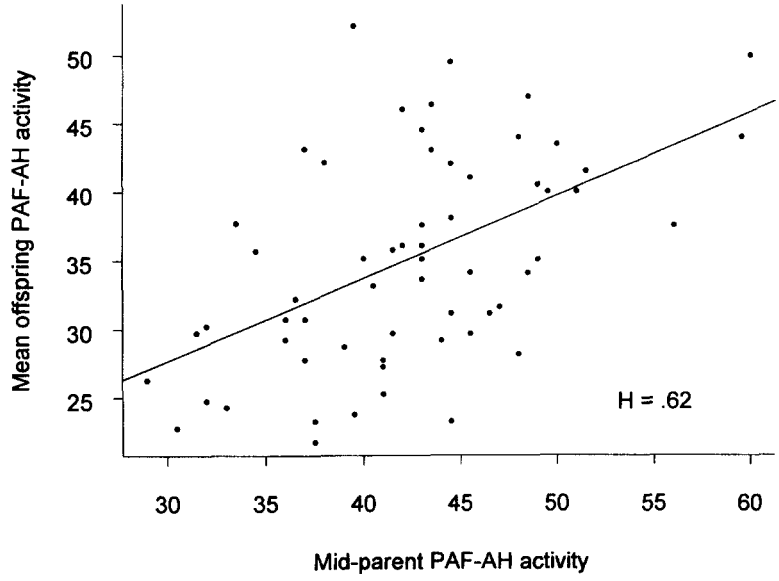

Fig. 2. Scatterplot of mean offspring plasma PAF-AH activity regressed against the mid-parent value. H is the slope of the regression line and indicates the heritability index.

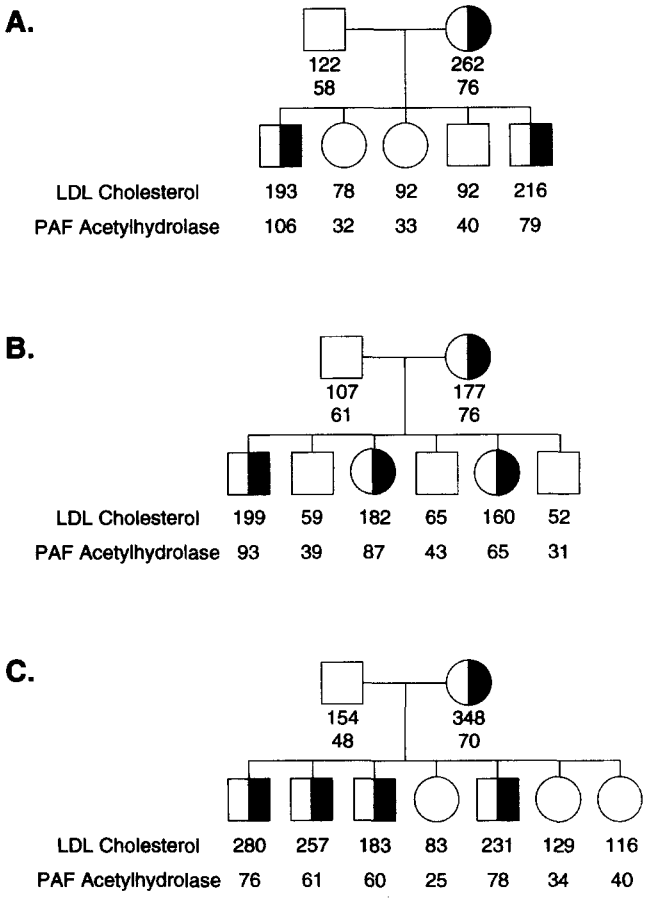

Fig. 3. Plasma PAF-AH activity and LDL-C concentrations in three families with familial hypercholesterolemia.

PAF-AH activity have not been identified. Like previous studies (11, 12) we found a strong correlation between plasma PAF-AH activity and plasma LDL-C concentrations. Therefore, it is possible that the observed heritability of plasma PAF-AH activity is a direct consequence of genetic variation in plasma LDL-C concentrations. To investigate this possibility, the heritability of plasma PAF-AH activity was determined after adjustment for variation in LDL-C. Plasma PAF-AH activity was linearly related to plasma LDL-C concentration, and simple linear regression adjustment eliminated variation due to LDL-C. The variance of the adjusted PAF-AH activities was 36% lower than the unadjusted values, indicating that variation in plasma LDL-C concentrations accounts for approximately one-third of the variance in PAF-AH activity. The heritability estimate based on the adjusted PAF-AH activities was almost identical to that obtained using the observed data, suggesting that a substantial fraction of the heritable variation in plasma PAF-AH activity is independent of variation in plasma LDL-C concentrations.

Two recent reports have indicated that major fraction of plasma PAF-AH activity is bound to lipoprotein [a] in plasma (20, 21). However, we have found no cosegregation of plasma PAF-AH activity and plasma concentrations of lipoprotein [a] in siblings with 50-fold differences in plasma lipoprotein [a] concentrations (H. Hobbs and V. Mooser, unpublished observations). Therefore the heritability of plasma PAF-AH activity is not due to genetic variation in plasma lipoprotein [a] concentrations.

To further elucidate the relationship between plasma concentrations of LDL and PAF-AH activity, we examined the segregation of PAF-AH activity in families with two well-characterized monogenic disorders of LDL metabolism: familial hypercholesterolemia (22) and familial hypobetalipoproteinemia (23). Familial hypercholesterolemia, an autosomal dominant trait caused by mutations in the LDL receptor gene, results in impaired clearance of plasma LDL and 2- to 3- fold elevated plasma LDL-C concentrations (22). We found that plasma PAF-AH activity was 2- to 3-fold higher in affected heterozygotes than in their unaffected siblings. Addition of exogenous LDL (up to 5-fold excess) to normal sera did not lead to increased PAF-AH activity, indicating that the elevated PAF-AH activity observed in familial hypercholesterolemia is not due to a direct effect of LDL on PAF-AH activity. In contrast to familial hypercholesterolemia where high LDL-C levels were associated with higher PAF-AH activities, individuals with familial hypobetalipoproteinemia had PAF-AH activities similar to their unaffected siblings. Indeed, some af-

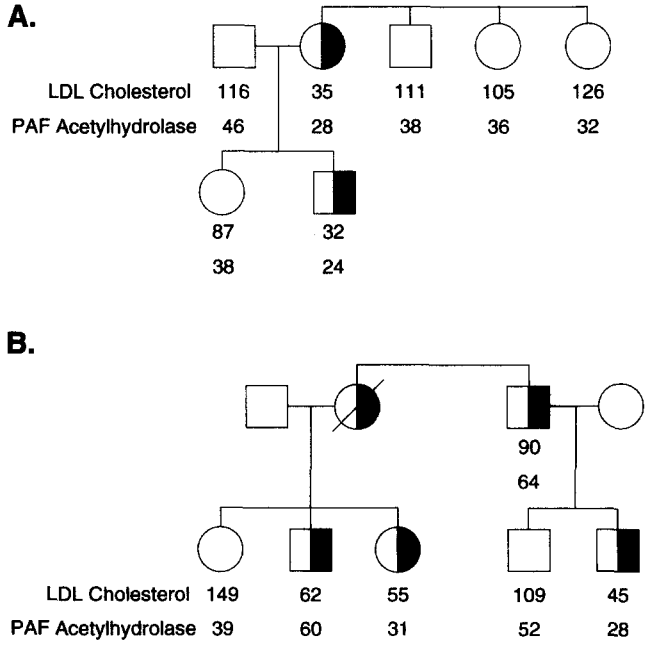

Fig. 4. Plasma PAF-AH activity and LDL-C concentrations in three families with familial hypobetalipoproteinemia.

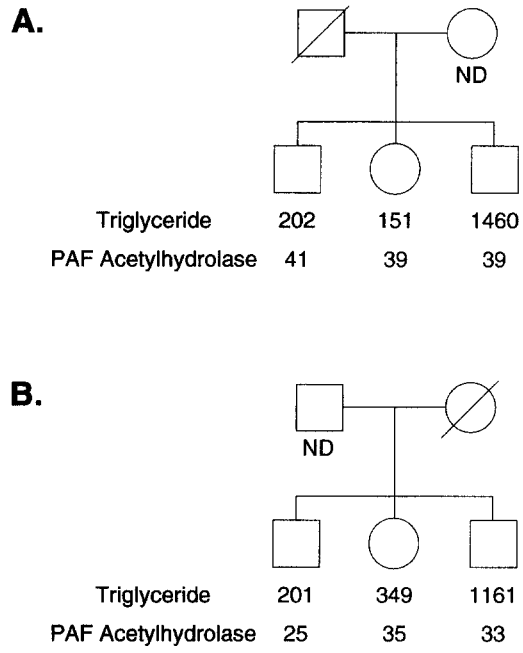

Fig. 5. Plasma PAF-AH activity and LDL-C concentrations in two hypertriglyceridemic probands and their siblings.

fected individuals in these pedigrees had relatively high PAF-AH activity, despite very low LDL-C concentrations. This result was surprising, given the strong correlation between plasma PAF-AH activity and LDL-C concentrations among normolipidemic individuals. Nonetheless, the results are consistent with previous observations that plasma PAF-AH activity is normal in patients with abetalipoproteinemia (13–15), and indicate that in these individuals, factors other than LDL-C have profound effects on plasma PAF-AH activity.

Taken together, these observations suggest that the correlation observed between plasma LDL-C concentration and PAF-AH activity reflects a process that influences both of these parameters. A hypothesis consistent with our findings is that plasma LDL-C concentration and PAF-AH activity are jointly influenced by the rate of LDL clearance. As the major fraction of PAF-AH is associated with LDL, the rate of removal of LDL from the circulation may determine the clearance rate of PAF-AH, and thus influence the amount and hence the activity of PAF-AH in blood. In familial hypercholesterolemia, LDL clearance is retarded and PAF-AH accumulates in the circulation. Plasma PAF-AH activity is therefore elevated. In contrast, lovastatin treatment accelerates LDL clearance (24), leading to increased removal of PAF-AH from the circulation and decreased plasma PAF-AH activity. In familial hypobetalipoproteinemia heterozygotes the clearance rate of LDL-containing truncated apolipoprotein B is accelerated, and almost all circulating LDL contains the normal apolipoprotein B isoform (23). As the molar ratio of LDL to PAF-AH is more than 100:1 in normal individuals (25), even heterozygous hypobetalipoproteinemic individuals have ample LDL for PAF-AH transport. Turnover studies in hypobetalipoproteinemic patients have indicated that the clearance rate of normal LDL is within the normal range in this condition (26, 27). Consequently, the residence time of PAF-AH should be normal in familial hypobetalipoproteinemia, and plasma PAF-AH activity is not reduced in proportion to the reduction in plasma LDL-C concentration in these patients.

LDL are formed in the circulation by sequential delipidation of VLDL (28, 29). PAF-AH activity has been found in VLDL (10, 12), and plasma PAF-AH activity was correlated with plasma triglyceride concentrations in our subjects (Table 1). Accumulation of VLDL in the circulation could therefore lead to increased PAF-AH activity. To test this hypothesis, PAF-AH activity was measured in plasma samples from siblings with extremely discordant levels of very low density lipoproteins. Plasma PAF-AH activity in patients with severe primary hypertriglyceridemia was indistinguishable from that of their unaffected siblings, indicating that elevated plasma VLDL concentrations do not lead to increased PAF-AH activity. Therefore the correlation observed between plasma PAF-AH activity and plasma triglyceride concentrations in unrelated individuals is unlikely to reflect a direct causal association between these two parameters. This finding also suggests that PAF-AH probably associates directly with LDL in the circulation, and

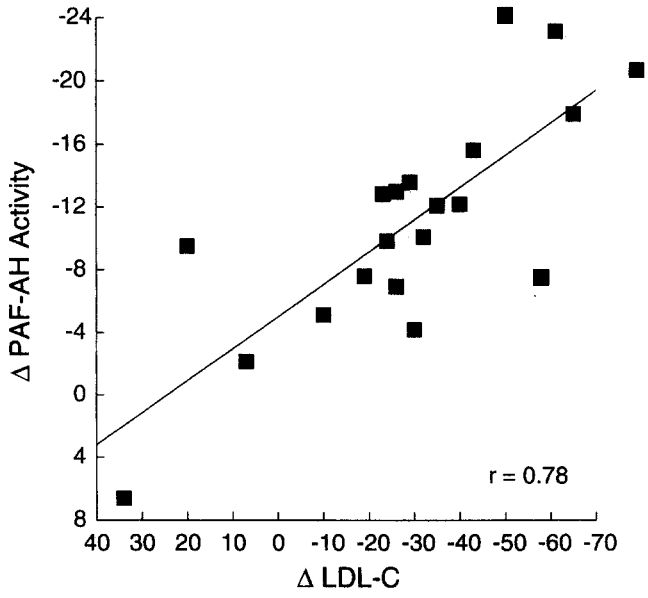

Fig. 6. Effect of 8 weeks of lovastatin treatment on plasma PAF-AH activity and plasma LDL-C concentrations. Values on both axes are the change from the baseline value.

is not brought into the LDL pool as a component of an LDL precursor.

In summary, the findings of the present study indicate that variation in plasma PAF-AH activity is strongly influenced by genetic factors. The specific genes involved remain to be determined, but they appear to be largely independent of those that confer heritable variation in plasma LDL-C concentration. Approximately one-third of the inter-individual variation in plasma PAF-AH activity is determined by plasma LDL-C concentrations, and some factors (such as lovastatin) that perturb LDL metabolism exert a proportional effect on plasma PAF-AH activity.

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