Plasma Platelet-Activating Factor Acetylhydrolase Activity in Human Immunodeficiency Virus Infection and the Acquired Immunodeficiency Syndrome

W. Khovidhunkit, R.A. Memon, J.K. Shigenaga, M. Pang, M. Schambelan, K. Mulligan, K.R. Feingold, and C. Grunfeld

Platelet-activating factor (PAF) acetylhydrolase (PAF-AH) catalyzes the hydrolysis of PAF, a mediator of inflammation, as well as other biologically active oxidized phospholipids. In humans, plasma PAF-AH activity is bound to low-density lipoprotein (LDL) and high-density lipoprotein (HDL). Higher levels of plasma PAF-AH activity have been found in a variety of diseases, and are thought to be a defense mechanism against the toxic effects of PAF and oxidized phospholipids. We studied plasma PAF-AH activity in patients with human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS), a disease characterized by chronic HIV infection and a systemic host response. Plasma PAF-AH activity was significantly greater in AIDS patients compared with control subjects (25.2 ± 2.0 *v* 17.0 ± 0.8 nmol/min/mL, $P < .001$). The higher levels of plasma PAF-AH activity were found in LDL (28.2 ± 2.2 *v* 18.3 ± 1.0 nmol/min/mL for AIDS *v* controls, respectively, $P = .0005$), but not in HDL. Plasma PAF-AH activity in AIDS correlated with circulating interferon alfa ($r = .575$, $P = .005$) and plasma triglycerides ($r = .556$, $P < .0025$). The presence of secondary infection in AIDS did not significantly change plasma PAF-AH activity. The initiation of a new antiretroviral regimen with either a protease inhibitor or the nucleoside analog lamivudine did not significantly decrease plasma PAF-AH activity, despite successful suppression of HIV RNA levels. Plasma PAF-AH activity may be a sensitive marker of the host response to infection, and the higher levels of plasma and LDL-associated PAF-AH activity in patients with HIV infection and AIDS may be a physiological response to protect the host against oxidative injury from PAF and oxidized phospholipids.

PLATELET-ACTIVATING FACTOR (PAF) is a phospholipid initially discovered as a factor released from activated basophils that causes platelet aggregation and degranulation.[1] It is now known that PAF-like activity is mediated by a group of structurally related phospholipid molecules, which are produced by a variety of cells and exert several biological activities including leukocyte activation, smooth muscle contraction, increased vascular permeability, and hypotension.[2,3] Most inflammatory cells, including polymorphonuclear leukocytes, monocytes, macrophages, platelets, and endothelial cells, produce PAF, suggesting that PAF is a mediator of immunologic and allergic reactions.

The activity of PAF is regulated by the enzyme PAF acetylhydrolase (PAF-AH).[4] PAF-AH degrades PAF by catalyzing the hydrolysis of the esterified acetate at the *sn*-2 position. Two forms of PAF-AH, encoded by different genes but demonstrating similar substrate specificity, are known to exist: the intracellular or cytosolic form and the plasma or secreted form. The intracellular form of PAF-AH has been found in the brain, liver, and kidney, whereas the plasma form circulates as a complex with lipoproteins.[4] In rodents, most of the plasma PAF-AH activity is found in high-density lipoprotein (HDL), whereas in humans, the majority (60% to 70%) of plasma PAF-AH activity is associated with low-density lipoprotein (LDL) and the remainder (30% to 40%) is in HDL.[5,6]

During inflammation, activated leukocytes, platelets, and endothelial cells generate PAF and oxidized phospholipids, both of which induce plasma PAF-AH production, providing a feedback regulation of the inflammatory response.[7-10] PAF-AH, in turn, degrades both PAF and the PAF-like oxidized phospholipids, protecting the host from injury due to these mediators.[11-13] The main cellular source of plasma PAF-AH activity remains controversial, and whether hepatocytes or macrophages are the primary source of plasma PAF-AH activity has not been established.[9,14-16]

The host response to infection and inflammation is characterized by marked alterations in hepatic protein synthesis. Changes of plasma PAF-AH activity have been observed in the presence of an acute-phase response, and therefore, PAF-AH can be viewed as one of the acute-phase proteins. However, the changes in these proteins vary among species and may differ among the types of stimulation. Injection of croton oil, for example, induced an acute-phase response in rabbits and decreased plasma PAF-AH activity,[17] whereas lipopolysaccharide (LPS) administration to rodents activated the host response and increased plasma PAF-AH activity.[16,18]

In humans, plasma PAF-AH activity is elevated in inflammatory diseases such as glomerulonephritis and rheumatoid arthritis.[19,20] However, in patients with sepsis, the results are contradictory.[21,22] In addition, patients with atherosclerosis including myocardial infarction, peripheral vascular disease, and ischemic stroke, as well as those with risk factors for atherosclerosis such as hypertension, familial hypercholesterolemia, diabetes, and cigarette-smoking, exhibited higher plasma PAF-AH activity.[23-31] The elevation in plasma PAF-AH activity is thought to

From the Metabolism Section, Medical Service, Department of Veterans Affairs Medical Center, San Francisco; Division of Endocrinology, Department of Medicine, San Francisco General Hospital, San Francisco; and Department of Medicine, University of California, San Francisco, San Francisco, CA.

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Address reprint requests to W. Khovidhunkit, MD, Department of Veterans Affairs Medical Center, 4150 Clement St (111F), San Francisco, CA 94121.

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protect the host against damage from PAF and oxidized phospholipids.

Human immunodeficiency virus (HIV) infection and the acquired immunodeficiency syndrome (AIDS) are associated with a systemic host response and several alterations in lipid metabolism.[32-34] These changes, including hypertriglyceridemia, decreased HDL, and the appearance of small dense LDL, are mediated by cytokines.[32-34] In the present study, we tested the hypothesis that chronic HIV infection is associated with an increase in plasma PAF-AH activity, and studied the effect of initiation of therapy with a protease inhibitor (PI) or the nucleoside analog lamivudine (3TC) on plasma PAF-AH activity.

SUBJECTS AND METHODS

Subjects

The study was performed under protocols approved by the Committee on Human Research of the University of California, San Francisco. The first group of subjects (n = 33) were recruited from the Infectious Diseases Clinic of the Department of Veterans Affairs Medical Center of San Francisco. All subjects were male, and each of the subjects had evidence of HIV infection as determined by the presence of antibodies against HIV measured by enzyme-linked immunosorbent assay (ELISA) and confirmed by Western blot. AIDS was identified on the basis of the revised criteria of the Centers for Disease Control.[35] Age-matched control subjects (n = 25) recruited from veterans groups and staff were also studied. These control subjects had no evidence of HIV infection by ELISA, had no ongoing medical illnesses, had normal physical examinations, and showed no symptoms or signs of infection at the time of study. None of the subjects had diabetes, renal failure, nephrotic syndrome, active hepatitis, or cirrhosis or took medication for treatment of hyperlipidemia at the time of the study.

The first group of AIDS patients was divided into two subgroups for analysis: those who were studied during a healthy period free of secondary infections (n = 28), and those who were studied during acute secondary infections (n = 16). Eleven subjects studied during the secondary infections were also studied at another time in the absence of any infection other than HIV itself. The acute secondary infections (n = 16) included acute sinusitis (n = 7), *Pneumocystis carinii* pneumonia (n = 5), *Mycobacterium avium* complex infection (n = 2), bacterial pneumonia (n = 1), and *Escherichia coli* urinary tract infection (n = 1). Healthy AIDS subjects were defined as those without fever, dyspnea, hypoxia, sputum production, sinusitis, urinary tract symptoms, positive urine culture, or positive blood culture as signs of secondary infection. Subjects were excluded from the healthy AIDS group if they had the symptoms or signs of acute infection just described.

The second group of subjects (n = 23) was a subset of patients participating in a natural history cohort study of HIV infection at the San Francisco General Hospital or studied at the Infectious Diseases Clinic of the Department of Veterans Affairs Medical Center at San Francisco. Each subject had evidence of HIV infection as determined by the detection of antibodies against HIV by ELISA and Western blot or by the presence of HIV RNA. A description of the patient population in the cohort study has been presented,[36] and details will be presented elsewhere.[37] This second group of patients was divided into two subgroups: those who were studied before and after receiving a protease inhibitor (PI) (n = 17), and those who were studied before and after receiving the nucleoside analog lamivudine (3TC) (n = 8). Two subjects who were treated with 3TC were subsequently studied before and after PI while on 3TC. Only plasma PAF-AH activity was determined in this second group of patients.

Plasma samples for measurements were drawn after a 10-hour overnight fast and stored at −70°C until the time of analysis.

Biochemical Determinations

Plasma PAF-AH was measured using a commercially available kit (Cayman Chemical, Ann Arbor, MI) according to the manufacturer's instructions. The assay uses 2-thio PAF as a substrate for PAF-AH. Upon hydrolysis of the acetyl thioester bond by PAF-AH, free thiols are detected using 5,5′-dithiobis-2-nitrobenzoic acid (DTNB, Ellman's reagent). The absorbance is read at 414 nm over a period of time using an ELISA plate reader. The detection range of the assay is 10 to 200 nmol/min/mL, and the assay is linear for at least 30 minutes. Recombinant PAF-AH (20 ng) was used as a positive control. Absorbance values were plotted as a function of time and PAF-AH activity was calculated from the linear portion of the curve.

Cholesterol and triglyceride concentrations were analyzed enzymatically (Sigma Diagnostics, St Louis, MO). HDL cholesterol was measured by the precipitation method as previously described.[33] LDL cholesterol was calculated by the method of Friedewald et al.[38] Direct quantitative determination of LDL cholesterol was performed using a LDL cholesterol kit (Sigma Diagnostics) as previously described.[39] Briefly, 200 μL LDL cholesterol reagent containing polystyrene latex beads coated with polyclonal antibodies to apolipoproteins A-I and E and 10 μL plasma were added to the inner compartment of a separation microcentrifuge tube and vortexed immediately. After incubation for 5 minutes, the mixture was centrifuged at 12,000× *g* for 5 minutes, which separated chylomicrons, VLDL, IDL, and HDL from LDL. LDL cholesterol was enzymatically assayed from the filtrate. Plasma apolipoprotein B-100 was measured by radial immunodiffusion as reported previously.[33]

Interferon alfa (interferon-α) levels were measured by a bioassay as previously described.[40] Circulating tumor necrosis factor (TNF) levels were analyzed by ELISA; C-reactive protein (CRP) and β_2-microglobulin levels were measured by radial immunodiffusion; and CD4 cell counts were measured by the UCSF Immunology Reference Laboratory as previously described.[33] HIV RNA levels in the second group of patients were determined by the Chiron (Emeryville, CA) Quantiplex HIV-1 RNA 2.0 branched DNA assay (detection limit, 500 copies/mL). HIV RNA levels in most subjects in the first group of patients were not available at the time of the study.

Isolation of Lipoproteins

Lipoproteins were isolated in 12 samples, six from the control group and six from the AIDS group, using a fast protein liquid chromatography (FPLC) system (Pharmacia Biotech, Piscataway, NJ) with two Superose 6 HR 10/30 columns connected in series as described previously.[41] Briefly, plasma was centrifuged at 12,000× *g* and a 0.5-mL aliquot of clear supernatant was loaded. Lipoproteins were eluted at a flow rate of 0.5 mL/min with a buffer (pH 7.4) containing 10 mmol/L NaH_2PO_4, 150 mmol/L NaCl, 1 mmol/L EDTA, and 0.02% (wt/vol) NaN_3. After the initial 12 mL was eluted, 60 fractions of 0.5 mL were collected. A total of 80 mL buffer was passed through the columns before the next sample was loaded. Cholesterol and triglyceride concentrations were analyzed by commercially available enzyme kits (Sigma Diagnostics) to identify the peaks of lipoprotein fractions. VLDL, IDL, LDL, and HDL fractions were pooled and concentrated using Centricon columns (Amicon, Beverly, MA) with a molecular weight cutoff of 10,000. PAF-AH activity was measured using 50 μL concentrated lipoprotein fractions.

LDL fractions were also isolated in all samples in the control group (n = 25) and in the healthy AIDS group (n = 28) by removal of other lipoproteins using the polystyrene latex beads coated with polyclonal antibodies to apolipoproteins A-I and E from the direct LDL cholesterol kit (Sigma Diagnostics) as already described. Direct LDL PAF-AH activity was measured using 50 μL of the LDL fractions.

Statistics

The results are presented as the mean ± SEM. Statistical significance for differences between two groups was determined using Student's *t* test when normally distributed. The Mann-Whitney test was performed when values were not in normal distribution. A paired *t* test was used for paired groups. Comparisons among several groups were made by ANOVA with statistical significance calculated using Bonferroni's test. Correlations were performed by linear regression analysis using Sigma Plot (Jandel Scientific, Corte Madera, CA).

RESULTS

PAF-AH Activity in Plasma and in Lipoprotein Fractions in AIDS

Baseline characteristics of the patients in group 1 are shown in Table 1. The mean plasma triglyceride concentration was higher and the mean plasma cholesterol, LDL cholesterol, and HDL cholesterol concentrations were lower in AIDS patients compared with controls. Similar differences have been observed previously.[32-34] In addition, we found no significant differences in plasma lipids between AIDS patients studied in the presence or absence of secondary infection (Table 1). Direct LDL cholesterol concentrations were in relative agreement with the LDL cholesterol concentrations calculated using the Friedewald formula ($r = .593$, $P < .0001$).

Because sepsis has been associated with changes in plasma PAF-AH activity,[21,22] we first compared plasma PAF-AH activity between healthy controls (n = 25) and healthy AIDS patients (n = 28). The mean plasma PAF-AH activity was significantly higher in healthy AIDS patients compared with controls (Fig 1A).

To determine the lipoprotein source of this elevation, lipoprotein was isolated and PAF-AH activity was measured in the lipoprotein fractions. Because PAF-AH can be transferred between lipoproteins (ie, LDL and HDL) and the transfer may occur during the lipoprotein isolation, we used two different methods, namely FPLC and immunoprecipitation, to isolate lipoproteins and measured PAF-AH activity in these lipoprotein fractions.

Lipoprotein isolation by the FPLC method was performed in 12 samples of plasma, six from control subjects (mean plasma PAF-AH activity, 17.2 nmol/min/mL) and six from healthy AIDS subjects (mean plasma PAF-AH activity, 33.1 nmol/min/mL). Ninety-five percent of the plasma PAF-AH activity was found in the LDL and HDL fractions; VLDL and IDL fractions contained a minute amount of PAF-AH activity (3.0% and 2.0% of the total plasma activity, respectively). LDL-associated PAF-AH activity was higher in the AIDS group compared with the control group (26.9 ± 4.3 *v* 9.8 ± 1.1 nmol/min/mL, $P < .0025$), but HDL-associated PAF-AH activity was not different from the control level (3.7 ± 0.6 *v* 3.4 ± 0.3 nmol/min/mL, $P = .94$).

To quantify LDL-associated PAF-AH activity in the entire cohort of subjects, we used an immunoprecipitation method instead of the laborious, time-consuming FPLC. VLDL and HDL were immunoprecipitated and PAF-AH activity was measured in the supernatant that contained LDL. The buffer of the LDL cholesterol kit used for immunoprecipitation had no significant effect on PAF-AH activity (data not shown). In AIDS patients, LDL-associated PAF-AH activity was 54% higher compared with the control group (Fig 1B). The result from the entire group of subjects confirmed the FPLC subset data that the change in plasma PAF-AH activity in AIDS patients was due to a higher LDL-associated PAF-AH activity. In addition, because PAF-AH activity in LDL fractions isolated by these two methods was similarly elevated in AIDS patients, the data suggest that the increase was not due to an isolation artifact.

Because AIDS patients have lower plasma LDL cholesterol compared with controls, a higher LDL-associated PAF-AH activity would indicate that PAF-AH activity was increased per LDL particle. LDL-associated PAF-AH activity expressed as nanomoles per minute per milligram LDL cholesterol was 2.3-fold higher in AIDS subjects compared with controls (Fig 1C).

In summary, plasma PAF-AH activity was higher in healthy AIDS subjects compared with controls, and the higher activity was due to LDL-associated PAF-AH, not HDL-associated PAF-AH.

Plasma PAF-AH Activity and Correlation With Plasma Lipids, Cytokines, and Acute-Phase Proteins

Alterations in lipid metabolism in AIDS are mediated by cytokines which may be mediators of the acute-phase response. We therefore measured the level of cytokines and acute-phase proteins in the healthy AIDS group. However, interferon α, TNF, CRP, and β_2-microglobulin levels were not available for all subjects and were determined in a subset of patients (n = 16 in the control group and n = 22 in the healthy AIDS group). Interferon-α was detected in 64% of AIDS patients; no controls

Table 1. Baseline Characteristics of AIDS Patients in Group 1

Characteristic	Control (n = 25)	AIDS (n = 28)	AIDS-SI (n = 16)	AIDS *v* Control	AIDS-SI *v* Control	AIDS-SI *v* AIDS
Age (yr)	43.4 ± 2.4	44.0 ± 1.6	45.3 ± 1.5	NS	NS	NS
CD4 cell count (per mL)*	ND	80.1 ± 20.2	60.3 ± 20.7	ND	ND	NS
Cholesterol (mg/dL)	194.4 ± 6.6	148.4 ± 8.5	139.0 ± 8.0	<.001	<.001	NS
Triglyceride (mg/dL)	109.5 ± 9.4	178.7 ± 16.8	169.5 ± 26.8	<.01	<.05	NS
HDL cholesterol (mg/dL)	46.5 ± 2.3	30.0 ± 1.6	24.6 ± 2.1	<.001	<.001	NS
LDL cholesterol (mg/dL)						
Calculated	126.0 ± 6.7	82.7 ± 7.5	80.5 ± 7.5	<.001	<.001	NS
Directly measured	100.9 ± 5.9	73.3 ± 6.2	ND	<.0025	ND	ND

Abbreviations: AIDS, healthy AIDS patients free of secondary infections; AIDS-SI, AIDS patients studied during acute secondary infections; NS, nonsignificant; ND, not determined.

*n = 25 in AIDS group and n = 16 in AIDS-SI group.

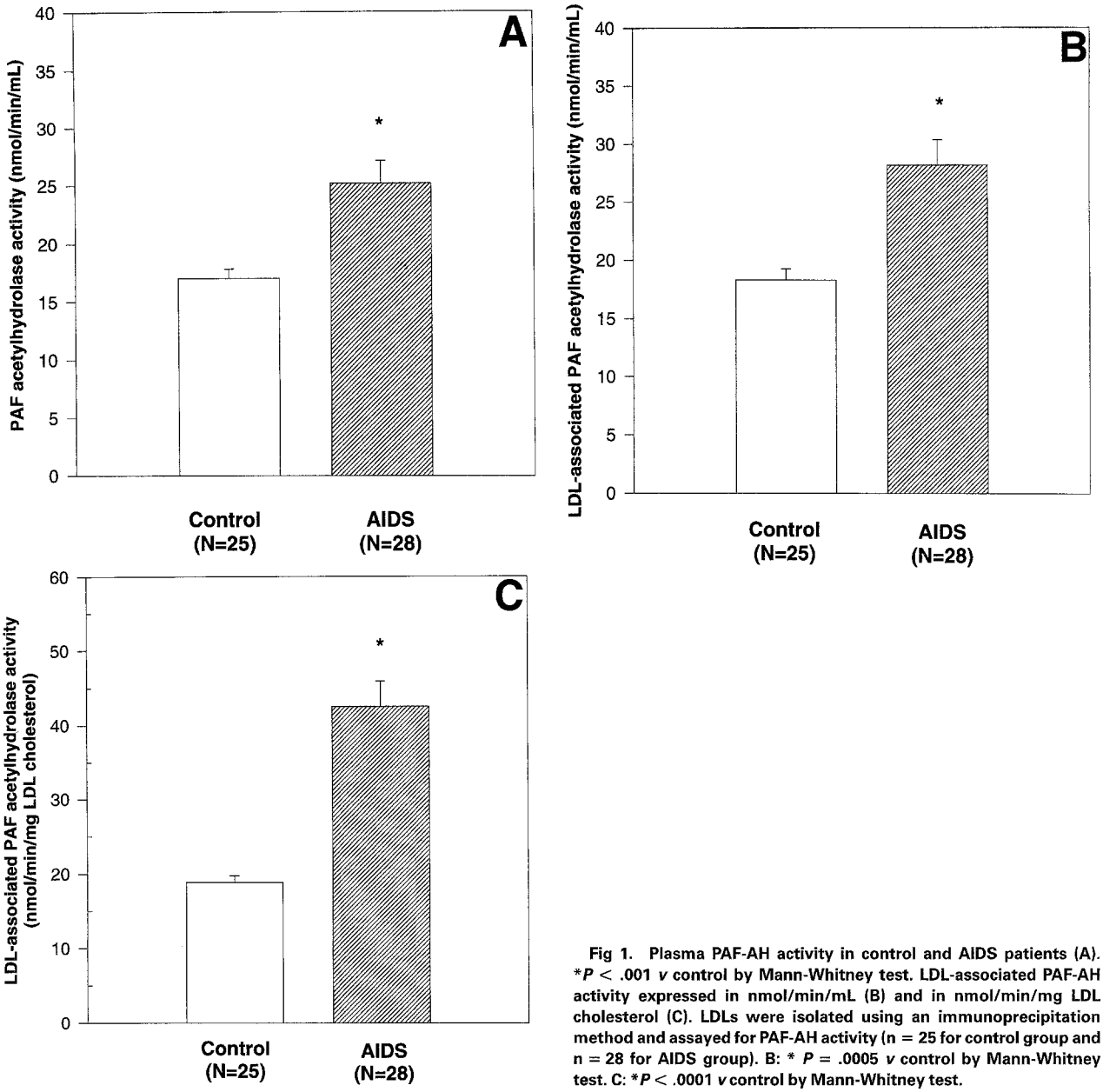

Fig 1. Plasma PAF-AH activity in control and AIDS patients (A). *$P < .001$ *v* control by Mann-Whitney test. LDL-associated PAF-AH activity expressed in nmol/min/mL (B) and in nmol/min/mg LDL cholesterol (C). LDLs were isolated using an immunoprecipitation method and assayed for PAF-AH activity (n = 25 for control group and n = 28 for AIDS group). B: * $P = .0005$ *v* control by Mann-Whitney test. C: *$P < .0001$ *v* control by Mann-Whitney test.

had detectable interferon-α levels (12.3 ± 3.5 *v* 0 U/mL). TNF was detected in 23% of AIDS patients and 13% of controls, and there was no difference between the groups (1.3 ± 0.5 *v* 2.1 ± 1.5 pg/mL, $P = .70$). Twenty-seven percent of AIDS patients had detectable CRP levels, but none was detectable in controls (0.2 ± 0.1 *v* 0 mg/dL). β_2-Microglobulin levels were higher in the AIDS group compared with controls (3.9 ± 0.3 *v* 1.4 ± 0.1 mg/L, $P < .0001$). Apolipoprotein B-100 levels were significantly lower in AIDS subjects compared with controls (59.8 ± 4.6 *v* 74.5 ± 4.3 mg/dL, respectively, $P < .05$).

In the AIDS group, there was a significant correlation between plasma PAF-AH activity and plasma interferon-α and triglyceride levels (Table 2 and Fig 2). There was no significant relationship between plasma PAF-AH activity in AIDS and the CD4 cell count, total cholesterol, LDL cholesterol, HDL cholesterol, TNF, CRP, or β_2-microglobulin levels.

Table 2. Correlation Between Plasma PAF-AH Activity and Plasma Lipid, Cytokine, and Acute-Phase Protein Levels in AIDS Patients

Parameter	*r*	*P*
Interferon-α	.575	.005
Triglyceride	.556	<.0025
CD4 cell count	−.129	NS
Total cholesterol	.313	NS
LDL cholesterol (measured)	.124	NS
Apolipoprotein B-100	.231	NS
HDL cholesterol	−.084	NS
TNF	.108	NS
CRP	−.277	NS
β_2-Microglobulin	.212	NS

Abbreviation: NS, nonsignificant.

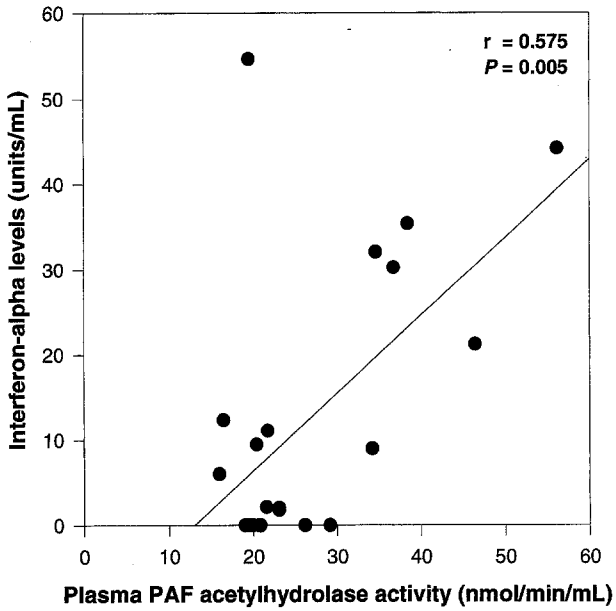

Fig 2. Correlation between plasma PAF-AH activity and plasma interferon-α levels ($r = .575$, $P = .005$).

Plasma PAF-AH Activity in AIDS and Acute Secondary Infection

It is known that bacterial infection in general provides a stronger stimulus to the acute-phase response than viral infection. For example, plasma concentrations of serum amyloid A, a well-known acute-phase response protein, are generally mildly elevated during viral infections but can become markedly elevated during bacterial infections. We therefore asked whether an acute secondary (bacterial or fungal) infection in chronic HIV-infected patients might change plasma PAF-AH activity further. We compared plasma PAF-AH activity between healthy AIDS subjects (n = 28) and AIDS patients during acute secondary infection (n = 16); however, we found no difference in plasma PAF-AH activity in AIDS patients with and without secondary infection (Fig 3A). Additionally, for patients who were studied during a secondary infection and at another time without the infection (n = 11), plasma PAF-AH activity was not significantly different (Fig 3B). Therefore, the presence of a secondary infection did not affect plasma PAF-AH activity in our AIDS subjects.

Effects of Antiretroviral Treatment on Plasma PAF-AH Activity

Baseline characteristics of the patients in group 2 are shown in Table 3. At baseline, there was no significant difference in plasma PAF-AH activity between the two subgroups. The mean interval between the two time points of follow-up study was 3.9 ± 0.6 and 3.9 ± 1.0 months in the PI and 3TC groups, respectively. Despite successful suppression of HIV RNA levels in AIDS patients who initiated therapy with a PI or 3TC (−1.4 ± 0.1 and −1.1 ± 0.3 $\Delta\log_{10}$ HIV RNA, respectively), we found that plasma PAF-AH activity did not significantly decrease in either group (Fig 4).

DISCUSSION

In the present study, we demonstrated that plasma PAF-AH activity is significantly greater in AIDS patients compared with controls and that the difference was in LDL, but not in HDL. In

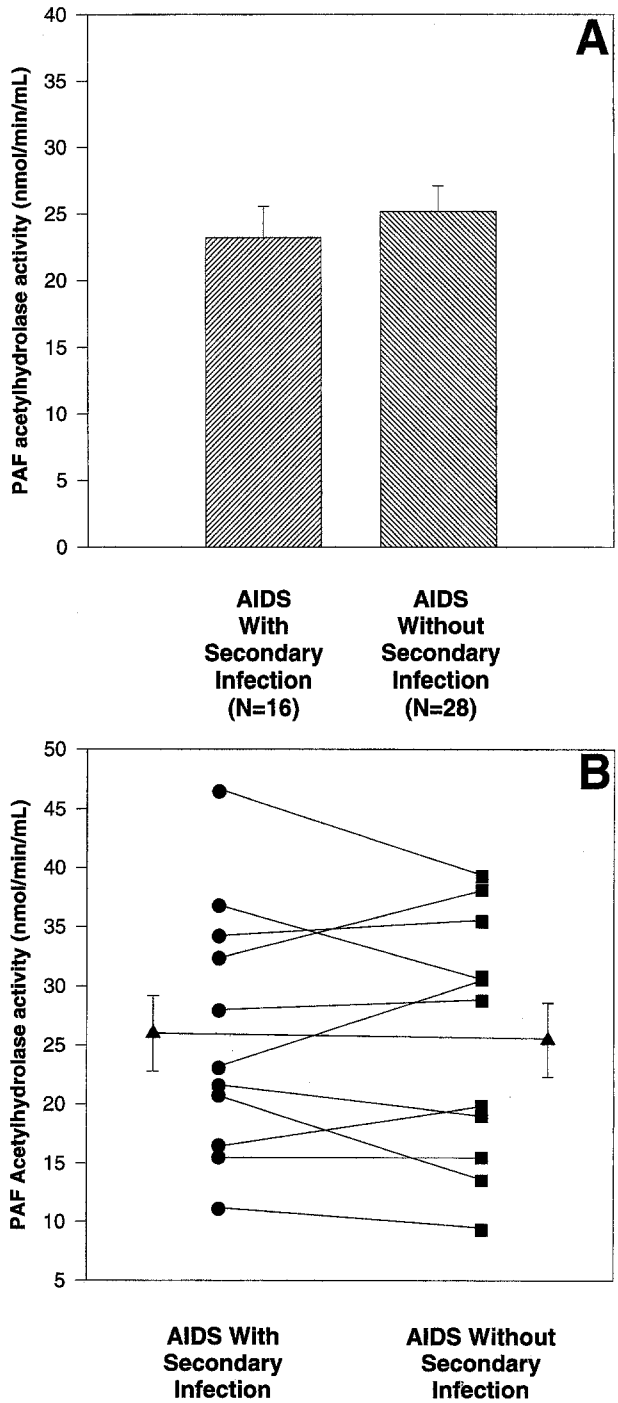

Fig 3. (A) Plasma PAF-AH activity in AIDS patients with and without secondary infection (n = 16 for AIDS with secondary infection and n = 28 for AIDS without secondary infection). $P = .54$. (B) Individual plasma PAF-AH activity in the same AIDS patients in the presence (●) and absence (■) of secondary infections (n = 11 for each group). $P = .74$. ▲, the mean in each group.

Table 3. Baseline Characteristics of HIV Patients in Group 2

Characteristic	PI (n = 17)	3TC (n = 8)
Gender (male/female)	15/2	7/1
Age (yr)	44 ± 2	45 ± 2
CD4 cell count (per mL)	167 ± 25	289 ± 80
HIV RNA (log_{10})	4.2 ± 0.1	4.7 ± 0.2
Cholesterol (mg/dL)	134.4 ± 6.0	132.6 ± 8.9
Triglyceride (mg/dL)	105.8 ± 12.1	107.4 ± 20.3
HDL cholesterol (mg/dL)	24.5 ± 1.6	24.7 ± 1.5
LDL cholesterol (mg/dL)		
Calculated	88.8 ± 5.2	84.0 ± 7.9
Directly measured	61.1 ± 4.3	60.1 ± 4.7

AIDS patients who developed acute secondary infections, there was no significant change in plasma PAF-AH activity, and in HIV-infected patients, plasma PAF-AH activity remained unchanged despite a successful suppression of HIV RNA levels after the initiation of a new antiretroviral regimen with either a PI or the nucleoside analog 3TC.

Alterations in plasma PAF-AH activity occur in animals during the acute-phase response which appear to be specific to the species and/or type of stimulation.[16-18] In humans, plasma PAF-AH activity is elevated in chronic inflammatory conditions.[19,20] Sepsis has also been shown to affect plasma PAF-AH activity, but contradictory results exist. There are reports that show an increase[22] or a decrease[21] in PAF-AH activity during sepsis.

AIDS is a chronic HIV infection that is associated with the systemic host response. Changes in plasma PAF-AH activity in AIDS suggest that PAF-AH could be one of the acute-phase response proteins. However, in AIDS patients who developed acute secondary infections, there was no further significant change in plasma PAF-AH activity, indicating that HIV infection may have already fully increased the plasma PAF-AH activity and acute secondary infection could not alter the degree of elevation. In addition, a successful suppression of HIV RNA levels by either a PI or 3TC was not accompanied by a lower level of plasma PAF-AH activity, suggesting that plasma PAF-AH activity may be a sensitive marker of the host response to infection.

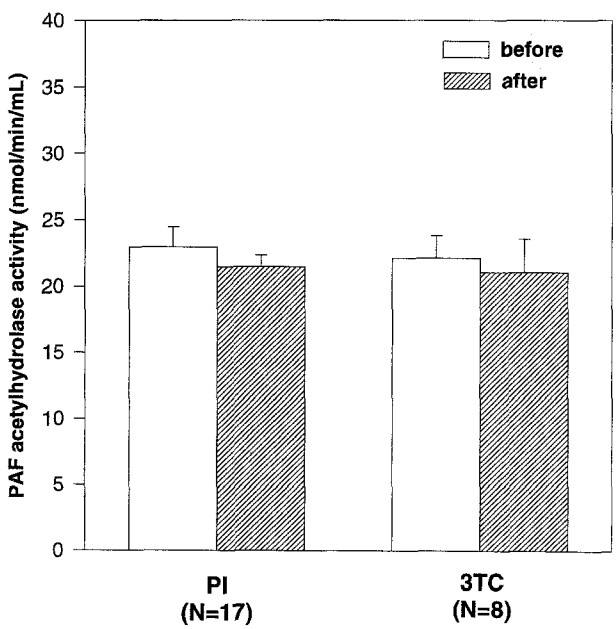

Fig 4. Plasma PAF-AH activity in HIV-infected patients before and after initiation of new antiretroviral therapy (PI and 3TC; n = 17 for the PI group and n = 8 for the 3TC group). Nonsignificant by paired *t* test.

Because the majority of plasma PAF-AH activity in humans is associated with LDL and HDL, alterations in plasma PAF-AH activity may occur due to changes in lipoprotein levels. In some conditions such as diabetes mellitus, a greater plasma PAF-AH activity has been attributed to an increase in plasma cholesterol,[30] and treatment with lovastatin produced a reduction in plasma cholesterol and PAF-AH activity.[28] However, the higher plasma PAF-AH activity in AIDS patients in our study cannot be explained by the relationship with the plasma lipids, since our AIDS patients had lower cholesterol and LDL cholesterol concentrations than normal subjects, and there was no relationship between plasma PAF-AH activity and plasma cholesterol, LDL cholesterol, or apolipoprotein B-100 concentrations.

The higher plasma PAF-AH activity in AIDS may occur by several mechanisms. Chronic HIV infection may activate the macrophage, one of the main cellular sources of plasma PAF-AH activity, and directly stimulate PAF-AH synthesis. Alternatively, HIV infection may result in generation of PAF and other oxidized phospholipids, which in turn stimulate plasma PAF-AH production. In fact, high levels of PAF were detected in the cerebrospinal fluid of AIDS patients, and PAF has been implicated in the pathogenesis of neurological dysfunction in AIDS.[42] In addition, both in vitro and in vivo studies have demonstrated that plasma PAF-AH activity is regulated by cytokines,[18,43] and changes in cytokine levels have been observed in AIDS. In our study, plasma PAF-AH activity in AIDS correlated with circulating interferon-α levels, which raises the possibility that the increase in PAF-AH activity may also be mediated by interferon-α. In vitro, interferon-α had no effect on the synthesis of plasma PAF-AH[43]; however, whether interferon-α induces plasma PAF-AH production in vivo is not known. Contradictory results obtained between in vitro and in vivo studies of LPS and cytokine regulation of plasma PAF-AH activity stress the importance of studying the regulation in an in vivo system.[16,18,43]

Plasma PAF-AH activity in our AIDS patients also correlated with plasma triglyceride concentrations. The underlying mechanism for this association is unclear; however, normal levels of plasma PAF-AH activity in patients with familial hypertriglyceridemia suggest that hypertriglyceridemia itself is not a direct cause of an increase in plasma PAF-AH activity.[28] Hypertriglyceridemia is a known metabolic disturbance occurring in AIDS and is mediated by cytokines. Circulating interferon-α levels, in particular, have been associated with hypertriglyceridemia in AIDS,[33,40] and interferon-α is known to affect lipid metabolism in rodents and humans.[44,45] It is possible that the increase in PAF-AH activity may involve interferon-α as in hypertriglyceridemia.

In addition to infection and inflammation, plasma PAF-AH activity is elevated in a variety of atherosclerotic diseases and in conditions predisposing to atherosclerosis such as hypertension,

hypercholesterolemia, diabetes, and smoking.[23-31] It is of note that atherosclerosis and these atherosclerotic risk factors are associated with vascular endothelial injury, which can increase PAF and oxidized phospholipids that stimulate PAF-AH synthesis. However, at present, the role of PAF-AH in atherosclerosis is unclear. Lipoprotein modification and oxidation is known to play an important role in atherogenesis, since it allows LDL to be recognized and taken up by macrophages to form foam cells, an early feature of atherosclerosis,[46] and oxidized LDL has been found in atherosclerotic lesions in both animals and humans.[47] PAF-AH can protect against oxidative damage from oxidized lipoproteins and also protects LDL particles from further modification in vitro.[13]

On the other hand, hydrolysis of oxidized phospholipids by PAF-AH generates lysophosphatidylcholine (LPC),[48] a molecule that may be responsible for various biological effects of oxidized LDL, including chemotaxis of monocytes, induction of adhesion molecules, impairment of relaxation of blood vessels, and smooth muscle cell and macrophage proliferation.[49-51] In animals, LPS injection increased both plasma PAF-AH activity and LPC concentrations.[18] In familial hypercholesterolemia, both increases in PAF-AH activity and LPC concentrations have also been observed.[27] Therefore, whether PAF-AH is beneficial to the host by protecting against oxidative injury or detrimental to the host by stimulating LPC formation is not known. It is possible that an acute increase in plasma PAF-AH activity may be beneficial to the host during infection, inflammation, and trauma, but chronic activation of PAF-AH activity would result in increased LPC formation and favor atherogenesis.

In summary, this study demonstrates that plasma PAF-AH activity is significantly greater in AIDS patients. The higher activity was found in the LDL and correlated with circulating interferon-α and plasma triglyceride levels. Neither the presence of secondary infections nor the initiation of therapy with a PI or 3TC, despite a suppression of HIV RNA levels, affected plasma PAF-AH activity.

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