Platelet-Activating Factor Acetylhydrolase in Plasma Lipoproteins From Patients With Ischemic Stroke

Kei Satoh, MD; Hidemi Yoshida, PhD; Tada-atsu Imaizumi, MD; Shigeru Takamatsu, MD; and Seitoku Mizuno, MD

Background and Purpose: Platelet-activating factor is a potent bioactive phospholipid and may play an important role in occlusive vascular diseases. To assess the inactivation of this autacoid in plasma, we measured platelet-activating factor acetylhydrolase activity in plasma low density and high density lipoproteins from patients with ischemic stroke.

Methods: Low density and high density lipoproteins were separated by ultracentrifugation from plasma of 33 patients with cerebral thrombosis and 31 age-matched healthy control subjects, and platelet-activating factor acetylhydrolase activity in each fraction was assayed.

Results: The average values of platelet-activating factor acetylhydrolase activity in low density lipoprotein from patients and control subjects were 41 ± 18 and 29 ± 17 nmol/ml per minute, respectively, and the difference was statistically significant (p < 0.01, U test). There was no difference in activity in high density lipoprotein between the two groups (16 ± 11 versus 14 ± 9 nmol/ml per minute, respectively).

Conclusions: The increased plasma platelet-activating factor acetylhydrolase activity in stroke patients is primarily attributable to the increased binding to low density lipoprotein, and this increase may be an adaptation to the augmented generation of platelet-activating factor in ischemic stroke. (Stroke 1992;23:1090-1092)

KEY WORDS • cerebral ischemia • lipoproteins • platelet-activating factor

Platelet-activating factor (PAF) is a bioactive phospholipid identified as 1-alkyl-2-acetyl-sn-glycero-3-phosphocholine. It is produced by various types of cells including neuronal cells1-3 and possesses neuroregulatory functions.4-6 Platelet-activating factor is inactivated by an enzyme called PAF acetylhydrolase, which removes the sn-2 acetyl moiety.7 There are intracellular and extracellular (plasma) forms of PAF acetylhydrolase,8 and in plasma this enzyme is associated with low density and high density lipoproteins (LDL and HDL).9 In our previous study we demonstrated age- and sex-related changes in the distribution of PAF acetylhydrolase activity among LDL and HDL in healthy subjects.10 The distribution of this enzyme among plasma lipoproteins may be of critical importance because the inactivation of PAF is achieved more effectively in LDL than in HDL.9 Although we previously observed an increased total plasma activity of this enzyme in stroke patients,11 the actual inactivation of PAF in plasma may also be affected by the relative distribution among LDL and HDL. Since PAF is known to play an important role in ischemic brain injury,12,13 inactivation of PAF may be one of the determinants of a pathophysiologica state after an ischemic event. Therefore, in this study we measured PAF acetylhydrolase activity in plasma LDL and HDL in patients with ischemic stroke.

Subjects and Methods

Subjects

The subjects studied included 33 consecutive patients (17 men and 16 women) with ischemic stroke, with an average age of 65 ± 9.9 years (mean ± SD). These patients were studied after their clinical condition had been stabilized (i.e., >2 months after the stroke). They did not receive any agents known to affect lipid or lipoprotein metabolism and platelet function. A computed tomographic scan was performed in all patients. Those who were diagnosed as having embolic stroke or lacunar infarcts were excluded from this study. The control group consisted of 31 healthy subjects (16 men and 15 women) who had participated in the annual health checkup program from April to October 1991. Their average age was 64 ± 8.7 years (mean ± SD). They had not received any medication during at least the preceding 4 weeks and did not show any abnormality in physical examination, urinalysis, chest x-ray film, electrocardiogram, and blood chemical and hematological screenings. Fasting venous blood was obtained in the morning using ethylenediaminetetraacetate as an anticoagulant.
TABLE 1. Platelet-Activating Factor Acetylhydrolase Activity in Plasma Lipoproteins of Stroke Patients and Control Subjects

<table>
<thead>
<tr>
<th>Lipoprotein</th>
<th>Patients</th>
<th>Control subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL</td>
<td>29±17</td>
<td>29±17</td>
</tr>
<tr>
<td>HDL</td>
<td>14±9</td>
<td>14±9</td>
</tr>
<tr>
<td>Total (LDL+HDL)</td>
<td>43±22</td>
<td>43±22</td>
</tr>
</tbody>
</table>

Values are mean±SD of platelet-activating factor (PAF) acetylhydrolase activity in 33 patients and 31 control subjects. Numbers in parentheses denote percentage of total activity. LDL, low density lipoprotein; HDL, high density lipoprotein.

PAF acetylhydrolase activity was significantly lower in stroke patients than in control subjects.

Discussion

The mechanism that regulates the distribution of PAF acetylhydrolase among lipoproteins is not clear. We have previously observed an increase in LDL-associated PAF acetylhydrolase activity with age-dependent increase in total plasma activity. Therefore, the capacity of the HDL fraction to bind PAF acetylhydrolase may be relatively limited and fixed, and the increase in total plasma activity may be attributable primarily to the increase in the binding of PAF acetylhydrolase to LDL.

TABLE 2. Plasma Levels of Lipids and Apolipoproteins

<table>
<thead>
<tr>
<th>Lipids or apolipoproteins</th>
<th>Patients</th>
<th>Control subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>192±42</td>
<td>195±42</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dl)</td>
<td>125±37</td>
<td>123±39</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dl)</td>
<td>41±12*</td>
<td>50±13</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>126±62</td>
<td>123±39</td>
</tr>
<tr>
<td>Apo A-I (mg/dl)</td>
<td>108±18*</td>
<td>136±24</td>
</tr>
<tr>
<td>Apo B (mg/dl)</td>
<td>117±27</td>
<td>128±31</td>
</tr>
</tbody>
</table>

Values are mean±SD of plasma lipids or apolipoproteins (Apo) in 33 patients and 31 control subjects. LDL, low density lipoprotein; HDL, high density lipoprotein.

PAF acetylhydrolase activity was significantly lower in stroke patients than in control subjects.

TABLE 3. Platelet-Activating Factor Acetylhydrolase/Cholesterol Ratio in Plasma Lipoproteins of Stroke Patients and Control Subjects

<table>
<thead>
<tr>
<th>Lipoproteins</th>
<th>Patients</th>
<th>Control subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL</td>
<td>37±19*</td>
<td>25±13*</td>
</tr>
<tr>
<td>HDL</td>
<td>43±32</td>
<td>32±30</td>
</tr>
</tbody>
</table>

Values are mean±SD of platelet-activating factor acetylhydrolase/cholesterol ratio (nmol/min per milligram) in low density lipoprotein (LDL) and high density lipoprotein (HDL) from 33 patients and 31 control subjects.

*<p<0.01 significantly lower than control value (t test).
the enzyme to LDL. Platelet-activating factor acetylhydrolase may be secreted by the liver as a complex with HDL, and in plasma it may be transferred to LDL. Higher activity in LDL may be advantageous for the inactivation of PAF in plasma because the inactivation proceeds more effectively in LDL than in HDL. Also, in our previous study we observed sex-related changes in LDL-associated PAF acetylhydrolase activity in healthy subjects. However, we did not find such differences in the present study, and this result is explained by the fact that enzyme activity in women had almost reached that in men by the sixth decade.

Recent studies have shown that PAF acetylhydrolase also hydrolyzes oxidized derivatives of phosphatidylcholine, which have a short chain acyl residue at the sn-2 position of the molecule. Such derivatives also exhibit PAF-like activity through binding to the PAF receptor. Although the occurrence in vivo of such phospholipid derivatives is not demonstrated, our previous study suggested the existence of bioactive phospholipids other than PAF in plasma from patients with ischemic stroke. It is also known that lipid oxidation is enhanced in stroke patients. Higher levels of PAF or PAF-like lipids may serve as a stimulus to increase the production of PAF acetylhydrolase by cells such as hepatocytes or macrophages, and the higher LDL-associated activity in stroke patients may be an adaptation to the increased generation of PAF or PAF-like lipids.

Lindsberg et al detected a substantial level of PAF bioactivity in the rabbit spinal cord subjected to ischemic injury. Platelet-activating factor induces differentiation, enhances the expression of c-fos and c-jun, and elevates intracellular Ca in neuronal cells. It may also act as a general membrane perturbant. All of these factors may influence brain injury in ischemic stroke. Therefore the rate of PAF inactivation in vivo may be of critical importance in determining the outcome of an acute ischemic event.

In conclusion, the activity of PAF acetylhydrolase in LDL is higher in stroke patients than in healthy control subjects, and this increase may not be due to the difference in the levels of plasma lipids or lipoproteins. In addition to the higher total plasma PAF acetylhydrolase, the increase in LDL-associated activity may favor the inactivation of PAF in plasma. Also, these results may be regarded as evidence of another aspect of LDL function.

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References

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