Plasminogen Interactions With Platelets in Plasma

By Burt Adelman, Alex Rizk, and Elizabeth Hanners

In this report we used a fluorescent flow cytometry–based assay to examine plasminogen binding to platelets in plasma. Our data indicate that platelets activated in platelet-rich plasma (PRP) by adenosine-5′-diphosphate (ADP) or thrombin bind plasminogen to their surface. Fab fragments of the monoclonal antibody LJ-CP8 that are directed against the fibrinogen binding site on the glycoprotein (GP) Ib-IX complex inhibit both plasminogen and fibrinogen binding to ADP-stimulated platelets. LJ-CP8, and iOE5 (an additional anti-GPIIb/IIa monoclonal antibody). The peptides Gly-Arg-Gly-Asp-Ser (GRGDS) when it is added to PRP before ADP stimulation. The scrambled peptide analogue SDGRG has no effect. The monoclonal antibody 6D1, directed against the von Willebrand factor binding site on GPIb, has no effect on platelet fibrinogen binding, nor does antithrombospondin antibody, ε-Aminocaproic acid (EACA), however, inhibits plasminogen binding to ADP-activated platelets. These data indicate that plasminogen binds to platelets activated in plasma, that binding occurs on platelet GPIb/IIa, and that binding may be mediated via plasminogen association with fibrinogen via lysine binding domains. Finally, we found both plasminogen and fibrinogen on resting platelets in PRP and demonstrated that they are equally displaced by EDTA, LJ-CP8, and 10E5 (an additional anti-GPIIb/IIa monoclonal antibody). Plasminogen is also equally displaced by EACA. These data suggest that plasminogen is also bound to GPIb/IIa on resting platelets, possibly also via interaction with fibrinogen.

P LASMIN is a relatively nonspecific protease generated during activation of the fibrinolytic system. In previous studies we observed inhibition of ristocetin-induced platelet agglutination following the addition of streptokinase to platelet-rich plasma (PRP) or plasmin to washed platelets. This effect was mediated by plasmin degradation of platelet glycoprotein Ib (GP Ib), a surface receptor for von Willebrand factor (vWF). We have also reported that treatment of washed platelets with concentrations of plasmin that occur during fibrinolytic therapy caused dose- and time-dependent inhibition of thrombin-, ionophore A23187–, and collagen-induced aggregation and thromboxane production. Other effects of plasmin on platelet function have also been reported. Schafer et al demonstrated that subinhibitory concentrations of plasmin and prostacyclin could work synergistically to inhibit platelet aggregation, and Loscalzo and Vaughan reported that tissue plasminogen activator treatment of platelets aggregating in plasma induced their disaggregation via plasmin generation.

Miles and Plow have demonstrated specific binding of plasmin and plasminogen to washed platelets. They determined that plasminogen binds to the fibrinogen receptor GPIb/IIa on resting platelets and that thrombin activation of washed platelets increases plasminogen binding. Because they did not observe plasminogen binding to adenosine-5′-diphosphate (ADP)-stimulated, washed platelets, they concluded that binding to thrombin-stimulated platelets was mediated via platelet-bound fibrin generated by thrombin. Their data also indicate that binding is mediated by lysine binding sites on plasminogen and that platelet-bound plasminogen can be activated to plasmin.

In this report we used immunofluorescent flow cytometry to directly assess plasminogen binding to platelets in plasma. Our data indicate that plasminogen binds to activated platelets and that the mechanism of binding is linked to basic events that occur during normal hemostasis. Thus, these studies further document platelet interaction with the fibrinolytic system during normal activation of hemostasis.

MATERIALS AND METHODS

Fluorescein isothiocyanate (FITC)- conjugated monospecific goat antiplasminogen IgG was obtained from Atlantic Antibodies, Scarborough, ME. Monospecific FITC-labeled goat antihuman fibrinogen, Fab(ab′)2, fragments of IgG, was purchased from Cappel Laboratories (Malvern, PA), as was nonspecific FITC-labeled goat IgG. Monospecific antithrombospondin antibody was provided by Drs Ralph Nachman and Adam Asch (Cornell Medical College, New York). The monoclonal antibody LJ-CP8 was provided by Dr Zavario Ruggeri (Scripps Clinic, La Jolla, CA) and 10E5 by Dr Barry Coller (State University of New York [SUNY], Stonybrook). LJ-CP8 and 10E5 each bind to platelet GPIb/IIa and block fibrinogen binding and platelet aggregation. The monoclonal antibody 6D1 was also supplied by Dr Barry Coller (SUNY, Stonybrook). 6D1 binds to platelet GPIb and blocks ristocetin-induced vWF binding. The peptides Gly-Arg-Gly-Asp-Ser (GRGDS) and Ser-Asp-Gly-Arg-Gly (SDGGR) were purchased from Sigma Chemical Co, St Louis. All other chemicals were reagent grade or better and were purchased from standard suppliers.

Plasminogen binding to resting and activated platelets. PRP was prepared by centrifugation of blood from normal donors anticoagulated in 0.38% sodium citrate (final concentration). Plasminogen binding to platelets was measured by fluorescent flow cytometry by using a method previously described. Briefly, resting or activated platelets in PRP were fixed by incubation with an equal volume of buffered 2% formaldehyde for 30 minutes at 37°C. After washing by centrifugation the platelets were resuspended in phosphate-buffered saline (PBS) (0.01 mol/L sodium phosphate, 0.15 mol/L NaCl, pH 7.4) and incubated on ice for 60 minutes with a saturating concen-
tation of antiplasminogen antibody or an equal concentration of nonspecific antibody. After incubation the platelets were washed by centrifugation, diluted to approximately 50,000/μL, and analyzed on an Ortho 50H flow cytometer equipped with a 5-W argon-ion laser and a 2140 data handling computer (Ortho Diagnostics, Westwood, MA). As previously described, the sizing gates were set to exclude platelet fragments and aggregates. The mean fluorescence intensity was determined by using log amplification. In each experiment 10,000 platelets were examined. Fibrinogen binding to platelets in PRP was similarly studied.

To measure plasminogen binding to activated platelets in plasma, PRP was incubated with 5 μmol/L ADP or with thrombin at room temperature. At various time points the reaction was stopped by the addition of buffered formaldehyde and the platelets processed as described earlier. To limit aggregate formation the PRP was only swirled once after the addition of either agonist.

Similar methods were used to study the inhibitory effects of various antibodies, ε-aminocaproic acid (EACA) and GRGDS on plasminogen binding to platelets. In these studies antibody, GRGDS, SDGRG, or EACA was added to PRP, and following activation, the platelets were formaldehyde fixed and processed as described earlier. To study the effect of calcium on plasminogen binding to platelets the calcium chelator EDTA was added to PRP warmed to 37°C. After incubation for 30 minutes at 37°C the platelets were either stimulated with ADP or fixed in a resting state and then processed as described earlier.

Platelet aggregation studies were performed in an aggregometer by the standard nephelometric technique described by Born and Cross.

RESULTS

We examined the binding of plasminogen to platelets in PRP stimulated by ADP. As seen in Fig 1, platelet-bound plasminogen levels increase rapidly following the addition of 5 μmol/L ADP to PRP; by three minutes plasminogen binding is 1.8 ± 0.1 (SE)-fold above basal. The addition of 0.2 U/mL thrombin to PRP increases plasminogen binding by 20%; however, the effect of higher concentrations of thrombin cannot be studied because it causes rapid clotting of PRP and prevents the isolation of individual platelets for analysis.

To identify the plasminogen binding site on ADP-stimu-

lated platelets we performed binding inhibition studies by using antibodies directed against the fibrinogen binding site on GPIIb/IIIa (LJ-CP8) and the vWF binding site on GPIb (6D1). The addition of Fab fragments of LJ-CP8 to PRP completely inhibited ADP-induced plasminogen-platelet binding (Table 1), whereas 6D1 had no effect. LJ-CP8 is used at a concentration that totally inhibits platelet aggregation by 5 μmol/L ADP and 6D1 at a concentration that totally inhibits ristocetin-induced (1.5 mg/mL) platelet agglutination.

Fibrinogen binding to GPIIb/IIIa is dependent on calcium ion, which functions to stabilize the receptor complex. Chelation of calcium at 37°C will disrupt the complex and prevent fibrinogen binding. To determine whether calcium is necessary for plasminogen binding to stimulated platelets we added EDTA to PRP before ADP activation. As seen in Table 1, 5 mmol/L EDTA totally inhibited plasminogen and fibrinogen binding to activated platelets.

The aforementioned results indicate that plasminogen binding to ADP-stimulated platelets is mediated by the GPIIb/IIIa complex and that disruption of the complex by calcium chelation inhibits binding. Thus, plasminogen binding appears to depend on mechanisms identical to those required for fibrinogen binding and platelet aggregation. To further characterize the relationship between platelet-fibrinogen binding and platelet-plasminogen binding we conducted studies in which fibrinogen binding to activated platelets was specifically blocked. Fibrinogen, but not plasminogen, contains the cell adhesion sequence GRGD. Binding of fibrinogen to ADP-stimulated platelets has been shown to depend on RGD-mediated attachment of fibrinogen to GPIIb/IIIa, while the addition of the RGD peptide or related analogues to platelet suspensions has been shown to inhibit fibrinogen binding and platelet aggregation. We therefore investigated the effect of the RGD analogue GRGDS on plasminogen binding to ADP-stimulated platelets. As seen in Fig 2, GRGDS concurrently blocked ADP-induced platelet aggregation and plasminogen binding at

![Fig 1. ADP-induced binding of plasminogen to platelets in PRP. ADP, 5 μmol/L, was added to PRP, and at the indicated time intervals the incubations were stopped by fixation and the platelets prepared for analysis of plasminogen binding by flow cytometry. Results are expressed as fold-increase in mean fluorescence. Each point represents the mean of three separate determinations of 10,000 platelets (± SE).](image-url)
Aggregation studies were conducted as described in Methods. Of 5 μmol/L ADP. After activation by ADP the platelets were fixed and analyzed by flow cytometry. Platelet aggregation studies were conducted as described in Methods. Each point represents the mean of two or three separate determinations. The scrambled analogue SDGRG had no effect on plasminogen binding or platelet aggregation. (•—•), plasminogen; (□—□), aggregation.

400 μmol/L GRGDS, both plasminogen binding and platelet aggregation were 90% inhibited. Fibrinogen binding, measured by flow cytometry, was inhibited 80% by 400 μmol/L GRGDS (Table 1). The scrambled peptide SDGRG has no effect on plasminogen binding or platelet aggregation when substituted for GRGDS in identical studies.

Plasminogen binding to some cell surfaces and to fibrin is mediated by its lysine binding region and can be blocked by lysine analogues such as EACA.24 We found that the addition of EACA to PRP reduces plasminogen binding to ADP-stimulated platelets and that a total inhibition of binding occurs at approximately 500 μmol/L EACA (Table 1 and Fig 3). Thrombospondin is a platelet α-granule protein secreted during platelet activation that binds to the platelet surface and stabilizes fibrinogen binding to GPIIb/IIIa.8 It has also been demonstrated that thrombospondin can bind plasminogen.25 Thus, we considered the possibility that thrombospondin could serve as a plasminogen binding site on activated platelets. We found, however, that the addition of antithrombospondin antibody to PRP before stimulation had no effect on plasminogen expression (Table 1). The antibody used in these studies blocks thrombospondin binding to the platelet surface and inhibits the irreversible component of ADP-induced platelet aggregation. The concentration of antithrombospondin antibody used in these experiments exceeds that necessary to maximally affect platelet aggregation as demonstrated by concurrently performed aggregation studies.

When using our assay method we detect plasminogen and fibrinogen on the surface of resting platelets in PRP. The mean fluorescence intensity of resting platelets stained with antiplasminogen antibody is fourfold greater than that of nonspecifically stained platelets. Similarly, the mean fluorescence of resting platelets stained with antifibrinogen antibody is also fourfold greater than that of nonspecifically stained platelets.

Because our assay method does not permit the use of analogue displacement techniques to differentiate between specific and nonspecific ligand binding, we can only examine that portion of binding that is mediated via known receptor sites. Thus, we decided to focus on determining whether a portion of the plasminogen associated with resting platelets was bound via interaction with GPIIb/IIIa and fibrinogen. We evaluated the effect of LJ-CP8, 10E5, 6D1, and EACA on plasminogen and fibrinogen binding to resting platelets and compared their effects with that of 5 mmol/L EDTA in the same system. We assumed that any fibrinogen or plasminogen displaced from resting platelets by EDTA was the result of dissociation of GPIIb/IIIa. The data from these experiments are listed in Table 2. Resting platelets incubated with EDTA released 32% ± 5% and 31% ± 8% (SE) respectively of their bound plasminogen and fibrinogen. The antibodies LJ-CP8 and 10E5 were almost as effective as EDTA in displacing plasminogen and fibrinogen from resting platelets. LJ-CP8 reduced fibrinogen binding on resting platelets 29% (91% of the effect of EDTA) and reduced plasminogen binding by 27% (84% of the effect of EDTA). The effect of 10E5 was equivalent to that of EDTA (100% of the effect of EDTA). EACA was 91% as effective as EDTA in displacing plasminogen and fibrinogen from resting platelets. LJ-CP8 and 10E5 were almost as effective as EDTA in displacing plasminogen and fibrinogen from resting platelets.

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We considered the possibility that the platelets become partly activated during processing and that the fibrinogen and plasminogen detected on resting platelets are bound ex vivo. However, when we assayed platelets obtained from blood drawn directly into anticoagulant containing 1 μg/mL prostaglandin E1 (PGE1) and 4 mmol/L theophylline, we did not detect a decrease in the amount of bound plasminogen and fibrinogen.

**DISCUSSION**

The results of this study indicate that plasminogen becomes bound to the surface of platelets stimulated in plasma. Our data also demonstrate that the primary binding site for plasminogen is the GPIIb/IIIa complex and that plasminogen binding to GPIIb/IIIa may be mediated by its attachment to fibrinogen via lysine binding regions. Plasmin-
PLASMINOGEN ON PLATELETS IN PLASMA

Table 2. Inhibition of Plasminogen and Fibrinogen Binding to Resting Platelets by Various Agents Relative to the Effect of EDTA

<table>
<thead>
<tr>
<th>Agent</th>
<th>Percentage of EDTA Effect on Plasminogen Binding</th>
<th>Percentage of EDTA Effect on Fibrinogen Binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDTA, 5 mmol/L</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>LJ-CP8, 260 µg/mL</td>
<td>91</td>
<td>84</td>
</tr>
<tr>
<td>10E5, 40 µg/mL</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>EACA, 500 µmol/L</td>
<td>91</td>
<td>ND</td>
</tr>
<tr>
<td>6D1, 20 µg/mL</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

For each experiment, PRP was incubated for 30 minutes with the agent listed or with buffer alone and then fixed, immunostained with FITC-antifibrinogen or antiplasminogen antibody, and analyzed by flow cytometry. Ligand binding was proportional to the mean fluorescence of the immunostained platelets. Agents that inhibit binding caused a reduction in mean fluorescence below that of platelets incubated with buffer alone. The effect of each agent was then compared with that of EDTA, and the results are expressed as a percentage of the effect of EDTA.

ND, no data.

*Experiments with EDTA were performed at 37°C.

Our studies also indicate that plasminogen is present on the surface of resting platelets in plasma, and the mechanism of binding appears, at least in part, to be identical to that for activated platelets. Although a previous study demonstrated that plasminogen can bind to washed platelets, no other report has documented that binding occurs in plasma following platelet activation by ADP.6,7

We find that when the synthetic peptide GRGDS blocks both fibrinogen and plasminogen binding to activated platelets, no other report has documented that binding occurs in plasma following platelet activation by ADP.6,7

Taken together, these studies indicate that plasminogen binds to GPIIb/IIIa on activated platelets near the fibrinogen binding site and that binding requires calcium. In addition, we observe that the addition of EDTA to platelets activated by ADP inhibits plasminogen and fibrinogen binding equally. Third, we find that the synthetic peptide GRGDS blocks both fibrinogen and plasminogen binding to activated platelets and that platelet aggregation was correspondingly inhibited by GRGDS.26

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The possible role of fibrinogen as an intermediary for elastase-mediated plasminogen binding in PRP is not an entirely new finding. Miles and Plow observed plasminogen binding to thrombin-activated washed platelets but not to ADP-activated washed platelets and concluded that only fibrin can serve as the intermediary for plasminogen binding.6,7 The assay methods used or reflect an interaction that occurs between fibrinogen and plasminogen in plasma that is not duplicated by addition of the purified proteins to washed platelets.

The nature of plasminogen interactions with fibrinogen is also present on the surface of resting platelets in plasma, and the mechanism of binding appears, at least in part, to be identical to that for activated platelets. Although a previous study demonstrated that plasminogen can bind to washed platelets, no other report has documented that binding occurs in plasma following platelet activation by ADP.6,7

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that we inadvertently removed this portion of bound plasminogen during processing for analysis. It is also possible that the plasminogen present on resting platelets that is not displaced by the various agents used in this study is not nonspecifically bound (as we currently suggest) but held in place by a mechanism that we have not identified.

It is difficult to know whether platelets removed from the circulation are identical to those in vivo, and we cannot be sure that resting platelets in the circulation bind any plasminogen or fibrinogen. We found that the addition of PGE, and theophylline to the anticoagulant mixture did not reduce the basal amount of plasminogen or fibrinogen on the surface of resting platelets. The addition of more potent antiplatelet agents such as prostacyclin might actually deactivate circulating platelets that are partially activated and carry appropriately bound fibrinogen and plasminogen. Thus, a final conclusion as to whether platelets circulate with plasminogen bound to their surface will require further investigation.

It is well recognized that the coagulation system is assembled and modulated by processes that are organized on surfaces. Recent studies by Mann and others have demonstrated a pivotal role for the platelet membrane in these events, particularly regarding the activation of thrombin by platelet-bound factors V and Xa. They reported that platelets are pro fibrinolytic and that platelet-dependent clot retraction is necessary for efficient fibrinolysis to occur. This report and others already mentioned indicate that platelets can provide a surface on which the fibrinolytic system can assemble and that platelet function can be modulated by plasmin. Further investigation of platelet interactions with the fibrinolytic system may shed additional light on the intrinsic regulation of thrombus formation and dissolution and may also assist in the development of better antithrombotic therapy.

REFERENCES


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