Two Receptor Systems Are Involved in the Plasma Clearance of Tissue Factor Pathway Inhibitor in Vivo*

Masaaki Narita, Guojun Bu, Gillian M. Olins, Darryl A. Higuchi, Joachim Herz, George J. Broze, J. R. S., and Alan L. Schwartz

From the Edward Mallinckrodt Departments of Pediatrics, Molecular Biology, and Pharmacology, the Division of Hematology/Oncology, Jewish Hospital at Washington University School of Medicine, St. Louis, Missouri 63110, the Department of Cardiovascular Diseases Research, G. D. Searle & Co., St. Louis, Missouri 63167, and the Division of Molecular Genetics, University of Texas Southwestern Medical Center at Dallas, Texas, 75235

Tissue factor pathway inhibitor (TFPI) is a potent inhibitor of the blood coagulation factor VIIa-tissue factor complex, as well as a direct inhibitor of factor Xa. Intravenously administered TFPI is rapidly cleared from circulation predominantly via liver. We previously reported that the low density lipoprotein receptor-related protein (LRP), a multifunctional endocytic receptor, mediates the uptake and degradation of TFPI in hepatoma cells. This process is inhibited by a 39-kDa receptor-associated protein which binds to LRP and regulates its ligand binding activity. However, a distinct, low affinity binding site (perhaps heparin sulfate proteoglycans, HSPGs) on the endothelium and liver is thought to be responsible for the majority of TFPI cell surface binding. In the current study, we investigated the role of LRP and this second binding site in the clearance of 125I-TFPI in vivo using competitors and inhibitors of the receptors. Mice expressing the 39-kDa protein via adenoviral-mediated gene transfer displayed diminished plasma clearance of 125I-TFPI. Blockade of cell surface HSPGs sites by incubation with the positively charged molecule, protamine, inhibited 125I-TFPI binding to the hepatoma cells in vitro. In addition, preadministration of protamine in vivo prolonged the plasma clearance of 125I-TFPI in a dose-dependent manner. However, a dramatic increase of the plasma half-life of 125I-TFPI and virtual elimination of 125I-TFPI clearance was observed in mice overexpressing the 39-kDa protein and administered protamine. Taken together, our results suggest that two receptor mechanisms are involved in the clearance of TFPI in vivo.

Tissue factor pathway inhibitor (TFPI) is a serine protease inhibitor that plays a key role in regulating tissue factor-initiated blood coagulation. Human TFPI is a 42-kDa plasma glycoprotein consisting of three tandem Kunitz-type domains, followed by a positively charged carboxyl terminus. The first Kunitz domain binds to and inhibits factor VIIa, and the second Kunitz domain binds to and inhibits factor Xa (2). Inhibition of tissue factor-induced blood coagulation by TFPI has been postulated to involve the quaternary factor Xa-TFPI-factor VIIa-tissue factor complex (3).

Intravenously administered 125I-TFPI is cleared rapidly from the circulation with a plasma half-life of 2 min in rabbits (4) and <1 min in rats (5). However, the biology underlying this clearance mechanism has not been elucidated to date. Previously, we demonstrated that the low density lipoprotein receptor-related protein (LRP) mediates the cellular degradation of TFPI in hepatoma cells (6) and that a 39-kDa protein, an inhibitor of all the ligand interactions with LRP (7), inhibits this process. In addition, cell surface heparin sulfate proteoglycans (HSPGs) associated with endothelial cells and liver have been proposed to play a role in the clearance of 125I-TFPI (8). However, the precise roles of LRP and HSPGs in the plasma clearance of TFPI have yet to be defined.

The purpose of the present study was to elucidate the roles of LRP and HSPGs in the catabolism of TFPI both in vivo and in vitro. We took advantage of viral-mediated gene transfer to express the 39-kDa protein in liver in vivo as such an approach has allowed us to define the role of LRP in the clearance of tissue-type plasminogen activator (t-PA) in vivo (9). The current results demonstrate a direct role for LRP as well as HSPGs in the plasma clearance of TFPI and thus suggest strategies for regulation of its catabolism.

MATERIALS AND METHODS

Reagents—Carrier-free sodium [125I]iodide was purchased from DuPont NEN. Bovine serum albumin was purchased from Calbiochem Co (La Jolla, CA). Protamine sulfate was purchased from Sigma. Porcine intestinal heparin for intravenous injection was from Elgin-Sinn Inc (Cherry Hill, NJ). IODO-GEN was from Pierce. BALB/c mice were obtained from Jackson Laboratories (Bar Harbor, ME). Sprague-Dawley rats were obtained from Harlan Sprague-Dawley Industries (Indianapolis, IN). Tissue culture medium was from Life Technologies, Inc. Protein A-agarose was purchased from Repligen Corp (Cambridge, MA). PE50 and PE205 were from Clay-Adams ( Parsippany, NJ). Inactin was purchased from BYK-Gulden (Constance, Germany).

Protein Iodination—TFPI was iodinated using IODO-GEN as described previously (10). Specific radioactivities were 5–10 Ci/mg of protein.

Purification of the 39-kDa Protein—Purification of the 39-kDa protein following expression in Escherichia coli was carried out as described previously (11). Cell Culture—Rat hepatoma MH3C1 cells were cultured as described previously (6).

Adenovirus Purification—Recombinant adenovirus containing the full-length rat 39-kDa protein cDNA (AdCMV-39-kDa) or the E. coli β-galacatosidase cDNA (AdCMV-β-Gal) were prepared and titered as described previously (9). The virus titer was approximately 100 virus particles/plaque-forming unit.

Binding Assay—125I-TFPI binding to MH3C1 cells was performed at
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4°C as described previously (6). Nonspecific binding was determined in the presence of excess unlabeled ligand as specified in the figure legend.

In Vivo Viral Delivery—In vivo viral delivery was performed via intravenous administration as described previously (9). Various viral particle doses were examined. Optimal expression was achieved following administration of 4 × 10^11 particles (4 × 10^10 plaque forming units) of either AdCMV-39-kDa or AdCMV-β-Gal (9). All experiments were performed on day 5 following virus delivery, since optimal expression of the 39-kDa protein was at day 4–5 following virus administration (9).

In Vivo Plasma Clearance in Mice—12–16-week-old BALB/c mice (weighing 20–25 g) were anesthetized with sodium pentobarbital (1 mg/20 g body weight mouse) during the course of the experiment. The indicated radiolabeled protein (34.0 pmol of 125I-TFPI) in sterile saline (total volume 100 μl) was injected into a tail vein over 30 s. In studies in which protamine was administered, the protamine was injected 1 min prior to administration of the radiolabeled TFPI. At the indicated times, 40–50 μl of blood was collected by periorbital bleeding. The amount of 125I-radiolabeled protein in the plasma samples was determined as described previously (12). Generally, at least three mice were independently evaluated for each clearance study, with essentially identical clearance curves within each experimental condition.

In Vivo Plasma Clearance in Rats—In vivo plasma clearance of unlabelled TFPI was evaluated in rats in the absence or presence of the recombinant 39-kDa protein as follows (12). One week before the experiment, PE50 catheters were implanted in the femoral artery and vein of Sprague-Dawley male rats (weighing 200–250 g). Blood samples (3 ml) were taken for establishing human TFPI/rat plasma standard curves. Rats were anesthetized with 100 mg/kg intraperitoneal injection of Inactin and placed onto servo-controlled heating pads to maintain body temperature between 37 and 38°C. The trachea was cannulated (PE205) to ensure airway patency. Following surgery, the animal was allowed to equilibrate for 10 min. An intravenous bolus of the 39-kDa protein (50 mg/kg, total volume 0.5 ml) or a similar volume of vehicle (saline) was injected, followed 1 min later by an intravenous bolus of human TFPI (0.5 mg/kg) in 0.5 ml of 20 mM sodium phosphate, pH 7.2. Blood samples were collected at −2, 1, 2, 3, 5, 10, and 40 min after injection. Blood was collected via the arterial catheter into tubes containing citrate, mixed, and then centrifuged to obtain plasma. The plasma was stored frozen at −80°C for later analysis. The concentration of TFPI antigen in plasma was measured by a particle concentration fluorescence immunoassay (13).

In Vivo Degradation of 125I-TFPI in Mice—The amount of 125I-TFPI in vivo was determined as follows; 90 min following administration of 125I-TFPI, both plasma and urine samples were collected. The 90-min time point was selected for analysis since preliminary observations demonstrated that degraded 125I-TFPI appeared initially 15 min after injection, increased over time, and peaked at 90 min (data not shown). Undegraded 125I-TFPI in both plasma and urine were precipitated by the addition of bovine serum albumin to 50 mg/ml and thereafter trichloroacetic acid to 20%. Degradation of 125I-TFPI was determined from the trichloroacetic acid-soluble radioactivity following correction for plasma urine volume.

Pharmacokinetic Analysis—The pharmacokinetic analysis of 125I-TFPI clearance in the presence or absence of various competitors was performed as described previously (9).

RESULTS

125I-TFPI Clearance in Normal Mice, AdCMV-β-Gal-injected mice, and AdCMV-39-kDa-injected mice—The plasma clearance of 125I-TFPI following intravenous administration of 34 pmol of 125I-TFPI in mice is shown in Fig. 1. The initial plasma halflife of 125I-TFPI was 30 s with <10% of the administered dose remaining in the circulation at 10 min (α phase t1/2 = 0.3 min, β phase t1/2 = 11 min). This clearance curve is similar to those described previously following intravenous administration of 125I-TFPI into rabbits (4, 14, 15), baboons (16), and rats (17).

To investigate the effect of LRP on 125I-TFPI clearance in vivo, we took advantage of the ability of the 39-kDa protein to inhibit 125I-TFPI interaction with LRP (6). In the current study, we used an adenoviral vector to carry the 39-kDa protein cDNA to be expressed in mouse liver. Overexpression of the 39-kDa protein results in plasma accumulation of the 39-kDa protein. Previously, we demonstrated that mice administered 4 × 10^11 particles of AdCMV-39-kDa expressed sufficient 39-kDa protein in plasma to completely inhibit LRP (9), and also demonstrated that viral infection induced no gross or microscopic morphological changes in the liver (9). This dose of AdCMV-39-kDa was administered intravenously to mice via tail vein. Five days after virus administration, mice were injected with 34 pmol of 125I-TFPI and plasma radioactivities were determined at the indicated times. Control mice (no administration of virus) are also shown. Clearance studies were determined for at least three mice in each group.

Effect of Recombinant 39-kDa Protein via Injection on the Plasma Clearance of 125I-TFPI—As described under “Materials and Methods,” either 4 × 10^11 particles of AdCMV-β-Gal or AdCMV-39-kDa were administered intravenously to mice via tail vein. Five days after virus administration, mice were injected with 34 pmol of 125I-TFPI and plasma radioactivities were determined at the indicated times. Control mice (no administration of virus) are also shown. Clearance studies were determined for at least three mice in each group.
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Effect of Injection of Recombinant 39-kDa Protein on the Plasma Clearance of TFPI in Rats

As described under “Materials and Methods,” rats were injected with 0.5 mg/kg intravenous of TFPI without (○) or with (●) preadministration of recombinant 39-kDa protein given as a bolus of 50 mg/kg intravenous. Clearance studies were determined for five animals in each group and are displayed as mean ± S.E.

Effect of Heparin and Protamine on the Clearance of 125I-TFPI in Normal and AdCMV-39-kDa-injected Mice—Recent studies have shown that administration of heparin resulted in increased plasma concentrations of TFPI in man (8) and in rabbit (14). This effect has been attributed to release of TFPI from HSPGs or glycosaminoglycan-binding sites along the endothelial and within the liver (5, 8, 14). Furthermore, administration of protamine following heparin reduced the TFPI activity in plasma to the preheparin value, presumably via neutralization of the administered heparin and reexposure of the endothelial/liver sites (18). Preliminary experiments demonstrated that administration of heparin to normal mice 10 min following the administration of 125I-TFPI resulted in a rapid (<1 min) rise in plasma 125I-TFPI to approximately the initial (i.e. zero time) level. This level was maintained for >30 min (data not shown). Similar observations were seen in mice administered AdCMV-39-kDAs. We next evaluated the effect of protamine on the clearance of 125I-TFPI in normal mice and AdCMV-39-kDa-injected mice following heparin administration. 100 units of heparin were administered 10 min after the administration of 125I-TFPI. Thereafter 1 min, 1 mg of protamine (a dose which neutralizes 100 units of heparin) was administered. As shown in Fig. 3, upon administration of protamine, there was rapid clearance of 125I-TFPI in normal mice. On the contrary, there was markedly prolonged clearance of 125I-TFPI following protamine administration in AdCMV-39-kDa-injected mice. These results suggest that the protamine not only neutralized the administered heparin but also was associated with additional effects on 125I-TFPI clearance.

Effect of Protamine and 39-kDa Protein on 125I-TFPI Binding to MH1C1 Cells in Vivo—Previously, we demonstrated that LRP mediates the cellular degradation of TFPI in hepatoma cells (6). LRP, however, does not appear to be the major cell surface receptor for TFPI, since 125I-TFPI binding at 4°C is not altered by the 39-kDa protein (6). This major binding species has been proposed to be HSPGs or glycosaminoglycans, as mentioned above. In order to determine whether these two receptor systems (LRP/HSPGs) function independently, we performed binding experiments with 125I-TFPI on MH1C1 cells in the presence of various competitors for these receptors. Since TFPI is thought to bind to the negatively charged HSPGs via its highly positively charged carboxyl terminus (19), and since heparin and other negatively charged molecules inhibit 125I-TFPI binding to MH1C1 cells at 4°C (5), we selected protamine as a potential competitor for HSPGs. As seen in Fig. 4A, binding of 125I-TFPI to MH1C1 cells at 4°C is not altered by the presence of the 39-kDa protein similar to our previous observations (6). However, as seen, protamine markedly inhibited 125I-TFPI binding in a dose-dependent manner. Next we eval-

![Image](44x525 to 296x742)

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FIG. 4. Effect of protamine and the 39-kDa protein on the binding of \(^{125}\text{I}-\text{TFPI}\) to \(\text{MH}_1\text{C}_1\) cells. A, cells were incubated for 2 h at 4°C with increasing concentrations of the 39-kDa protein (●) or protamine (○). Thereafter, the cell monolayers were washed to remove unbound ligand and directly lysed to determine cell-associated radioactivity. Radioactivity was converted to femtomole equivalents of \(^{125}\text{I}-\text{TFPI}\) calculated from the specific activities and is normalized per well. Each symbol represents the average of duplicate determinations. B, cells were incubated for 2 h at 4°C with increasing concentrations of the 39-kDa protein in the presence of 100 \(\mu\text{g/ml}\) protamine and processed as in A.

FIG. 5. Effect of preadministration of AdCMV-39-kDa and protamine on the clearance of \(^{125}\text{I}-\text{TFPI}\) in vivo. Various doses of protamine (0.01, 0.1, and 1 mg) were administered 1 min prior to the injection of 34 pmol of \(^{125}\text{I}-\text{TFPI}\) to either normal mice or mice which had received 4 \(\times\) \(10^{11}\) particles of AdCMV-39-kDa 5 days earlier. Plasma \(^{125}\text{I}-\text{TFPI}\) radioactivities were determined at the indicated times. Clearance studies were determined for at least three mice in each group.

DISCUSSION

The present observations demonstrate that 1) inactivation of LRP in vivo by gene transfer of a 39-kDa protein prolongs the plasma half-life of \(^{125}\text{I}-\text{TFPI}\), especially the \(\beta\) phase, 2) in vivo degradation of exogenously administered TFPI is inhibited about 50% by inactivation of LRP by the 39-kDa protein, 3) in vitro the 39-kDa protein inhibits the binding of \(^{125}\text{I}-\text{TFPI}\) to hepatoma cells in a dose-dependent manner under conditions in which \(^{125}\text{I}-\text{TFPI}\) is unable to bind to HSPGs, 4) blockade of HSPGs by administration of protamine in vivo prolongs the plasma half-life of \(^{125}\text{I}-\text{TFPI}\), and 5) a dramatic increase in the plasma half-life of \(^{125}\text{I}-\text{TFPI}\) is observed in mice overexpressing the 39-kDa protein and administered protamine, a competitor for the HSPGs-binding sites. Taken together, these results indicate that in vivo LRP mediates the degradation of \(^{125}\text{I}-\text{TFPI}\) and that both LRP and HSPGs are responsible for \(^{125}\text{I}-\text{TFPI}\) clearance.

TFPI is a potent inhibitor of the factor VIIa-tissue factor complex as well as a direct inhibitor of factor Xa. In addition, in animal models TFPI is a potential therapeutic agent in vivo for tissue-thromboplastin-induced intravascular coagulation and prevention of arterial reocclusion after thrombosis (20, 21). Of the many parameters which govern the plasma level of TFPI, its clearance and catabolism play a central role. Elucidation of the molecular basis thereof has recently begun. Using hepatoma cell lines, we reported recently that LRP mediates TFPI degradation (6). The cellular degradation of \(^{125}\text{I}-\text{TFPI}\) was inhibited \(>80\%\) both by antibodies directed against LRP and by the LRP-associated 39-kDa protein. LRP, however, does not appear to be the major cell surface receptor for TFPI, since \(^{125}\text{I}-\text{TFPI}\) binding at 4°C was not inhibited by the 39-kDa protein (6). This major binding species has been proposed to be HSPGs or glycosaminoglycans, as mentioned above. Circumstantial evidence suggests that TFPI may be bound to heparan

evaluated the ability of the 39-kDa protein to affect \(^{125}\text{I}-\text{TFPI}\) binding in the presence of protamine. As shown in Fig. 4B, in the presence of protamine, the 39-kDa protein inhibited \(^{125}\text{I}-\text{TFPI}\) binding to \(\text{MH}_1\text{C}_1\) cells in a dose-dependent manner. Thus, protamine reduced \(^{125}\text{I}-\text{TFPI}\) binding by \(\sim 90\%\) from 800 to 80 fmoi/well while the 39-kDa protein reduced binding an additional \(\sim 70\%\) (from 80 to 20 fmoi/well). This observation is consistent with our earlier estimate that \(\text{MH}_1\text{C}_1\) cells express 3 times as many TFPI-binding sites (2 \(\times\) \(10^6\) sites/cell) as LRP-binding sites (6). Therefore, it is likely that a small fraction of \(^{125}\text{I}-\text{TFPI}\)-binding sites are inhibited by the 39-kDa protein (Fig. 4A), but is below the sensitivity of the assay.

Effect of Protamine on \(^{125}\text{I}-\text{TFPI}\) Clearance in Normal Mice and AdCMV-39-kDa-injected Mice—To examine whether the mechanisms proposed in vitro are expressed in vivo, we performed clearance studies of \(^{125}\text{I}-\text{TFPI}\) using various concentrations of protamine as competitors for the HSPGs sites. As seen in Fig. 5, preinjection of various amounts of protamine (0.01, 0.1, and 1 mg) reduced the plasma half-life of \(^{125}\text{I}-\text{TFPI}\) from less than 1 min to 1–2 min. The fraction of \(^{125}\text{I}-\text{TFPI}\) remaining in the plasma at 10 min was 3% (no protamine), 5% (0.01 mg), 8% (0.1 mg), and 13% (1 mg), respectively. We next combined the administration of the competitors for these two receptor systems. As seen in Fig. 5, preadministration of protamine (1 mg) to AdCMV-39-kDa-injected mice dramatically prolonged the plasma half-life of \(^{125}\text{I}-\text{TFPI}\) compared to that observed with either competitor alone (Figs. 1, and 5). The average half-life of \(^{125}\text{I}-\text{TFPI}\) in these mice was \(\sim 10\) min with \(>70\%\) remaining in the plasma at 10 min. These results indicate that LRP and HSPGs function independently as clearance receptors for \(^{125}\text{I}-\text{TFPI}\) in vivo.
sulfate proteoglycans on the endothelial or liver cell surface. This hypothesis is based on the observations that (a) TFPI binds to heparin-agarose (22); (b) heparin and sulfated polysaccharides enhance the anticoagulant activity of TFPI (19); and (c) after intravenous administration of heparin, plasma levels of TFPI increase severalfold (8, 15).

After the intravenous administration of 125I-TFPI in mice, TFPI was rapidly cleared from the circulation ($\alpha$ phase $t_{1/2} \sim 0.3$ min, $\beta$ phase $t_{1/2} \sim 11$ min). LRP and/or HSPGs are thought to be responsible for this clearance. Administration of 39-kDa protein either directly by injection or via gene delivery as AdCMV-39-kDa altered the clearance of TFPI, especially the $\beta$ phase (Figs. 1 and 2). However, the effect of 39-kDa protein on TFPI clearance is not as significant as that seen for 125I-t-PA following the 39-kDa administration via infusion (12) or via AdCMV-39-kDa (9). LRP is responsible for the majority of t-PA clearance (over 50%) (10, see Figs. 1 and 3), whereas for TFPI, LRP is not the major clearance receptor. This may be because of the difference in the number of total binding sites available to TFPI or other LRP-specific ligands. The observation that MH1C2 hepatoma cells appear to have $\sim 10$ times as many 125I-TFPI-binding sites ($2 \times 10^{6}$ sites/cell) as binding sites for the LRP-specific ligands tissue-type plasminogen activator and $\alpha_2$-macroglobulin (6) supports this hypothesis.

Previously, we have demonstrated that the 39-kDa protein inhibited 125I-TFPI degradation by $\sim 80\%$ in hepatoma cells (5, 6). In the current study, in AdCMV-39-kDa-infected mice, intravenously administered 125I-TFPI degradation was inhibited $\sim 50\%$. This observation deary demonstrates that LRP mediates degradation of 125I-TFPI in vivo as well. As expected, 125I-TFPI degradation (i.e. fragment accumulation) was inhibited more significantly in urine than in serum (Table I). Since the sites of TFPI clearance in vivo are the liver and kidney (4, 5), the 39-kDa protein may inhibit LRP activity in kidney as well as in liver. Alternatively, kidney gp330, an LRP homolog which is also inhibited by the 39-kDa protein (23), may function in TFPI clearance, as well.

Previously, we reported that the 39-kDa protein did not inhibit TFPI binding to hepatoma cells (6). However, as seen in Fig. 4 in the presence of protamine, which competes for 125I-TFPI binding to cell surface HSPGs, the 39-kDa protein inhibits the binding of 125I-TFPI to MH1C2 cells in a dose-dependent manner. The effect of protamine on inhibition of 125I-TFPI binding to MH1C2 cells is nearly saturated at 100 $\mu$g/ml of protamine. Under these conditions, binding of 125I-TFPI to MH1C2 cells is approximately 10% as that found without protamine. These results are thus consistent with those above. In addition and consistent with the in vitro results, administration of protamine decreased the plasma half-life of 125I-TFPI in vivo in a dose-dependent manner. In the presence of 1 mg of protamine, a dramatic increase in the plasma half-life of 125I-TFPI ($\sim 10$ min) was observed in mice overexpressing the 39-kDa protein. These results clearly demonstrate that two independent receptor systems are involved in the clearance of 125I-TFPI (one protamine-sensitive, i.e. HSPGs; the other 39-kDa protein-sensitive, i.e. LRP). Furthermore, they demonstrate that while the endothelial/liver cell surface HSPG-bindings sites for TFPI are important in clearance of TFPI from the plasma, this sequestered TFPI is readily releasable and ultimately available back in the plasma.

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