PROTEOLYTIC DEGRADATION of fibrin clots (fibrinolysis) is mediated by the enzyme plasmin. Plasmin is formed in the circulation from the inactive precursor plasminogen through the proteolytic action of plasminogen activators (PA). For both plasmin and plasminogen activators specific inhibitors are present: α2-antiplasmin and plasminogen activator inhibitors (PA-inhibitors), respectively.

Proteinase inhibitors represent nearly 10% of the total protein in blood plasma. They control a variety of critical events associated with connective tissue turnover, coagulation, fibrinolysis, complement activation, and inflammatory reactions. As a general rule, proteinase inhibitors can react with several proteinases. The attribution of a specific function to a certain proteinase inhibitor depends on its concentration and its second-order rate constant with a certain proteinase; these two parameters determine the half-life of a proteinase due to inactivation by the inhibitor. As early as 1963 Brakman and Astrup claimed the existence of PA-inhibitors by demonstrating a fibrinolytic inhibitor that did not inhibit plasmin in the blood of pregnant women. Several reports about the presence of a specific inhibitor of PA in human plasma have appeared before 1982; however, due to the lack of appropriate kinetic data, a specific inhibitor of PA in blood plasma has never been convincingly demonstrated. The question has been raised whether there is a logical function for specific PA-inhibitors at all, since the activity of PA is regulated by several mechanisms such as release from the vessel wall and rapid hepatic clearance, specific interaction with fibrin (at least for tissue-type PA [t-PA]) and proteolytic activation of single-chain PA (at least for prourokinase). Moreover, the activity of the fibrinolytic system is strongly regulated by the abundant plasmin inhibitor α2-antiplasmin (0.06 mg/mL plasma). Nevertheless, the existence of specific PA-inhibitors is now no longer a matter of dispute. PA-inhibitors can already be classified in at least three immunologically different groups: the endothelial cell type PA-inhibitor (PAI-1), the placental type PA-inhibitor (PAI-2), and protease nexin-I. Their function in the regulation of the activity of the fibrinolytic system is still only partly understood. This review is not meant as a historical or chronological review, but briefly summarizes what is presently known about PA-inhibitors.

Endothelial cell–type PA-inhibitor (PAI-1) is synthesized by endothelial cells and human hepatocytes in culture, by several hepatoma cell lines, granulosa cells, SV-40 virus–transformed human lung fibroblasts (the cell line WI-38 VA 132 RA), the MJZJ melanoma cell line, and probably by vascular smooth muscle cells; it is also found in the α-granules of blood platelets and plasma. This inhibitor reacts with both urinary-type plasminogen activator (u-PA) and t-PA, with a second-order rate constant of above 10^6 to 10^7 mol/L⁻¹ s⁻¹. The reaction of the inhibitor with these PA eventually results in the formation of sodium dodecyl sulphate (SDS)-stable complexes with a molecular mass that is 40 to 50 kilodaltons (kd) higher than the molecular mass of the free PA. The PA/PA-inhibitor complex has no PA activity as such, but after SDS/Triton X-100 treatment a PA activity can be generated that is much smaller than the activity of an equivalent quantity of free PA. Whether this is due to dissociation of a small part of the PA/PA-inhibitor complex molecules induced by the SDS/Triton X-100 treatment or due to an intrinsic activity of the complex after SDS/Triton X-100 treatment is not yet clear. Endothelial cell–conditioned medium and blood platelets contain both active and inactive (latent) forms of PAI-1. The PA-inhibitor is probably synthesized by cultured endothelial cells in an active form. Inactivation (apart from complex formation with PA) can occur in at least two different ways: by a rapid inactivation of newly synthesized PA-inhibitor upon leaving the cell, with a calculated half-life of 0.29 hour; and by a much slower inactivation in (cell-free) conditioned medium with a half-life of two to four hours at 37°C. Whether the rapid and slow inactivation processes also take place in vivo is not yet clear. The accumulation of the inactive (latent) form in 24-hour endothelial cell–conditioned medium, reaching up to a hundredfold excess of inactive over active PA-inhibitor, is probably due to inactivation of actively synthesized PA-inhibitor. The inactive (latent) form does not inhibit t-PA or u-PA, nor does it form complexes with these PA. This inactive form can, however, be “activated” in vitro by the action of protein denaturants such as SDS, urea, and guanidine HCl, followed by renaturation through removal of the...
In contrast, the half-life of t-PA in blood plasma due to inactivation by α2-antiplasmin is 90 to 180 minutes. PAI-1 detectable in blood plasma is indistinguishable from the inhibitor in endothelial cell-conditioned medium with regard to t-PA second-order rate constants. The molecular mass of PA/PA-inhibitor complexes and apparent dissociation constants. The origin of PAI-1 in blood plasma has not yet been established. Although of course the endothelial cell is a good candidate, primary cultures of human hepatocytes also synthesize this inhibitor. Furthermore, blood platelets contain this type of PA-inhibitor. This latter “cell”, however, probably does not contribute to the plasma level of PAI-1 under physiological conditions.

PA-INHIBITOR TYPE 2

In human placenta an inhibitor of u-PA and t-PA is present. This inhibitor was first described by Kawai et al in 1968. It has now been purified to homogeneity from placental tissue. The inhibitor has a molecular mass of 48 kilodaltons, as judged by gel filtration and SDS-PAGE and forms complexes with both the high–molecular weight and the low–molecular weight form of u-PA, with two-chain t-PA, and to a lesser extent with single-chain t-PA. A monoclonal antibody of the IgG type against this inhibitor has been obtained. Recently, Kruijhof et al have purified to homogeneity a PA-inhibitor from the human histiocytic lymphoma cell line u-937. This PA-inhibitor is immunologically related to the PA-inhibitor from placenta. This u-937 derived PA-inhibitor has a molecular mass of 47 kd as judged by SDS-PAGE and reacts with both u-PA and t-PA to form SDS-stable complexes with a molecular mass about 40 kd higher than that of the free PA. This inhibitor, like the inhibitor purified from placental tissue, reacts better with two-chain t-PA with a higher k0) with two-chain t-PA than with single-chain t-PA.

The cellular origin of the PA-inhibitor in placenta is at present not known. It has been established that a macrophage-derived cell line produces PAI-2. Moreover, several authors have reported the synthesis of a PA-inhibitor by primary cultures of human macrophages of different origin. Although the immunologic relationship with PAI-2 has not yet been established, the macrophage-derived PA-inhibitor shows functional similarity to PAI-2, in that it reacts much better with u-PA than with single-chain t-PA. It has been proposed, therefore, that the PA-inhibitor from human placenta is of macrophage origin.

The concentration of the active inhibitor in blood plasma in healthy subjects shows a large interindividual variation and ranges from 0.0 to about 1.3 nmol/L. At a PA-inhibitor concentration of 1 nmol/L and with a second-order rate constant of 106 mol/L·s−1, the half-life of PA in plasma due to inactivation by the inhibitor is about 100 seconds, which is well in the physiologically important range.

Fig 1. The fibrinolytic system. Fibrin can be proteolytically degraded into soluble fibrin degradation products by the action of plasmin. Active plasmin is formed from its inactive zymogen plasminogen by the proteolytic action of PA. The dotted bar pointing toward PA represents proteolytic processing of single-chain PA into two-chain PA, a process that tremendously changes the catalytic properties of urokinase but affects the catalytic properties of t-PA in a minor way. The cascade is specifically inhibited at the level of plasmin by α2-antiplasmin and at the level of PA by PA-inhibitors.
PROTEASE NEXIN

Protease nexin I has been purified to homogeneity from human foreskin fibroblast-conditioned medium. It has a molecular mass of about 43 kd and contains approximately 6% carbohydrate. It is a broad specificity inhibitor of trypsin-like serine proteinases. It reacts rapidly with trypsin (k₀ = 4.2 × 10⁶ mol/L⁻¹s⁻¹), thrombin (k₀ = 6.0 × 10⁵ mol/L⁻¹s⁻¹), u-PA (k₀ = 1.5 × 10⁵ mol/L⁻¹s⁻¹), single-chain t-PA (k₀ = 1.5 × 10⁴ mol/L⁻¹s⁻¹), two-chain t-PA (k₀ = 3.0 × 10⁴ mol/L⁻¹s⁻¹), and plasmin (k₀ = 1.3 × 10⁵ mol/L⁻¹s⁻¹), forming 1:1 complexes with these proteinases. It contains a high-affinity heparin binding site; in the presence of heparin the rate of the reaction of protease nexin I with thrombin is nearly diffusion-controlled.

Protease nexin I is synthesized by a number of anchorage-dependent cells including fibroblasts, heart muscle cells, and kidney epithelial cells. In serum-free cultures of human fibroblasts, secreted protease nexin I suppresses the cellular sensitivity to the mitogenic action of added thrombin. It limits activation of secreted single-chain u-PA by exogenous proteinases and inhibits two-chain u-PA.

Fibroblasts bear surface receptors that mediate the endocytosis and lysosomal degradation of protease nexin I complexes. Protease nexin I is not detectable in blood plasma. Since the second-order rate constants of protease nexin I with thrombin and trypsin are much higher than with either t-PA or urokinase, protease nexin I cannot be considered a true PA-inhibitor. Also, because data on protease nexin I concentrations are lacking, a calculation of a half-life of plasminogen activators due to inactivation by protease nexin I cannot be made.

PHYSIOLOGY OF PA-INHIBITORS

PA play a central role in a number of physiologic processes. Of these, the fibrinolytic system has received the most attention. For this reason, most literature on PA-inhibitors deals with the role of these inhibitors in the homeostasis of the circulation. Very little is known about the function of PA-inhibitors in the many other physiologic processes in which PA are involved (tissue repair, nidation, fertilization, cell proliferation, etc).

In most studies, only PA-inhibitory activity has been measured in assays based on titration of PA-inhibitors with PA. The reader should be cautioned that the interpretation of these assays is not always easy, since increased PA-inhibitory activity can be caused by either increased PA-inhibitor or decreased PA. Also in most studies immunologic data on the type of PA-inhibitor are lacking. For this reason we use in this review the vague term “PA-inhibitory activity” when more precise data are lacking. Otherwise the term will be more specified.

In pooled normal human blood plasma PAI-2 and protease nexin I are not found. About 60% of the PA-inhibitory activity is PAI-1. The remaining 40% is attributed to a so far limitedly characterized factor, designated as PA-binding protein.

The PA-inhibitory activity in blood plasma of healthy individuals is subject to a diurnal fluctuation: lowest values are found at 3:00 PM. Moreover, there is a large interindividual variation of plasma PA-inhibitory activity levels (at 9:00 AM) ranging from 0.0 to 1.3 nmol/L. On the other hand, the 9:00 AM value of plasma PA-inhibitory activity of a certain individual is constant for at least several weeks (Sprengers et al, unpublished results, January 1986). As mentioned before, the cellular origin(s) of the plasma PA-inhibitor has not yet been established.

In vitro, PAI-1 is not stable at 37°C. Incubation of endothelial cell-conditioned medium, partly purified inhibitor, or plasma at this temperature leads to a first-order decrease of PA-inhibitory activity with a half-life of two to four hours. Activated protein C and thrombin inactivate the PA-inhibitory activity in endothelial cell-conditioned medium, an effect that is at least partly due to a direct effect of activated protein C (and thrombin) on the inhibitor. Activated protein C can form 1:1 complexes with PA-inhibitor. This process may contribute to another linkage of the coagulation and the fibrinolytic system. The antithrombotic effect of activated protein C mediated by inhibiting the coagulation pathway may thus be enforced by its profibrinolytic potential.

PA-inhibitory activity is very rapidly cleared from the circulation; half-lives of seven minutes in the rabbit and 3.5 minutes in the rat have been reported. The inhibitory activity is cleared at a much slower rate during liver ligation, suggesting that clearance takes place primarily in the liver, as is true also for PA. It is interesting to note that though the steady state level of PA-inhibitor is several orders of magnitude lower than that of the major plasma proteinase inhibitors, this short half-life suggests that the rate of synthesis of PA-inhibitor is approximately of the same order of magnitude as of the major plasma proteinase inhibitors.

PAI-1 in blood plasma behaves as an acute-phase reactant protein. PA-inhibitory activity rapidly increases after major surgery, myocardial infarction, and severe trauma. We observed that PA-inhibitory activity was only increased on the first postoperative day, thus being the most rapidly reverting acute-phase reactant protein described so far. Other authors observed a much more slowly reverting pattern. According to the latter authors, the acute-phase response parallels the response of cortisol after extensive surgery. The administration of adrenocorticotropic (ACTH), however, induces cortisol to the same extent while leaving PA-inhibitory activity unaffected. This excludes a simple cause–effect relationship between increased cortisol and PA-inhibitory activity levels.

PA-inhibitory activity in plasma is also induced by infusion of a single dose of bacterial wall lipopolysaccharide (endotoxin) or interleukin-1. The increase is optimal in about four hours and is reverted within 24 hours. Lipopolysaccharide and interleukin-1 added to endothelial cell culture yield a tremendous increase in PA-inhibitory activity in the conditioned medium of the endothelial cells. It is significant that interleukin-1 does not increase PA-inhibitory activity in the conditioned medium of hepatocytes and the human hepatoma cell line Hep G2, suggesting endothelial cells rather than liver as the source of increase in PA-
inhibitory activity in plasma by the acute-phase reaction mediator interleukin-1.79 Thrombin added to confluent monolayers of human endothelial cells resulted in a sixfold increase in PA-inhibitory activity in 24-hour-conditioned medium, an effect that was dependent on RNA and protein synthesis.80 Although PA-inhibitor antigen was not assessed in this study, the authors suggest that because t-PA antigen was also increased, the increase in PA-inhibitory activity was due to an increased amount of PA-inhibitor antigen. Since thrombin inactivates PA-inhibitory activity in endothelial cell-conditioned medium79 this observation can only be explained by assuming that the increased rate of synthesis of PA-inhibitor is higher than the increased rate of inactivation. Indeed, we recently demonstrated that low concentrations of thrombin added to endothelial cell cultures increase both PAI-1 antigen and activity in the conditioned medium, whereas high concentrations of thrombin increase PAI-1 antigen but decrease its activity in the conditioned medium due to proteolytic degradation of the inhibitor (Van Hinsberg et al, unpublished data, September 1986).

Long-term oral administration of the synthetic anabolic steroid stanozolol to human volunteers decreases the PA-inhibitory activity in blood plasma.62 At least 3 weeks are required for maximal suppression of PA-inhibitory activity using a dosage of 10 mg/day.62 Treatment with stanozolol, 10 mg orally per day for 2 weeks preoperative, significantly enhanced the fibrinolytic activity before surgery but did not prevent the decline in fibrinolytic activity which occurs after surgery.83 In cell culture the synthetic corticosteroid dexamethasone induces PA-inhibitor in HTC rat hepatoma cells.51,16 However, in the human hepatoma cell line Hep G2 dexamethasone does not influence the secretion of PAI-1.14

During pregnancy, PA-inhibitory activity gradually increases up to tenfold at the end of the third trimester.54-56 Postpartum it rapidly returns to prepregnant values. In “at risk” pregnancies (preeclampsia, suspected fetal growth retardation, diabetes mellitus, thrombosis and/or a previous history of thrombosis) a considerably wider range of PA-inhibitory activities, including much higher values, is observed.84 Using an immunologic assay, a gradual increase in PAI-2 has been reported during pregnancy, yielding values up to 100 μg/mL in the third trimester and rapidly returning to prepregnant values after delivery.57 Moreover, by immunoabsorption using a monoclonal anti-PAI-2 antibody, PA-inhibitory activity can be isolated from pregnancy plasmas, suggesting that PAI-2 in pregnancy plasmas is at least partly active.59 Unfortunately, in this study no data on the molecular forms or specific activity (units/mg antigen) of the PA-inhibitor are given; so a precise interpretation of the data, ie, whether all the antigen represents active PA-inhibitor, is not possible. Our results indicate that the increase in PA-inhibitory activity during pregnancy as assessed by a titration assay can be almost fully quenched by a specific anti-PAI-1 antibody (Sprengers et al, unpublished data, April 1985).

Several authors studied associations of PA-inhibitory activity levels with certain states of disease. The most intensively studied pathologic state so far is deep venous thrombosis. Three groups independently established that deep venous thrombosis is frequently (but not necessarily) associated with high PA-inhibitor levels.87-90 Paramo et al recently found that preoperative levels of PA-inhibitory activity were significantly higher in patients that developed postoperative deep venous thrombosis.91 On the other hand, deep venous thrombosis is also frequently associated with an impaired release of t-PA from the vessel wall.87-88 These data indicate that impaired fibrinolysis can play a role in the pathogenesis of deep venous thrombosis. In patients with myocardial infarction several investigators have found an increased PA-inhibitory activity together with a decreased level of t-PA activity or antigen.29,31,34 In patients with coronary artery disease, the increase in the level of the PA-inhibitory activity did not correlate with the severity of the disease, however.59 High PA-inhibitory activity levels are positively correlated with hyperlipoproteinemia.69 Other authors found a correlation between high PA-inhibitory activity levels and serum triglycerides.79 Juan-Vague et al found increased PA-inhibitory activity levels in the plasma of critically ill patients with a variety of diseases: pancreatitis (four of eight), liver disease (three of eight), malignancy (five of 26), myocardial infarction (five of 28), and deep venous thrombosis (two of nine).29 Kruithof et al also reported an increased PA-inhibitory activity in an even wider variety of hospitalized subjects.82 To the contrary, in terminal renal insufficiency, either in patients with nonfunctioning kidneys in situ or without kidneys, PA-inhibitory activity was not significantly different from normal values.86

The general picture emerging is that increased PA-inhibitor levels in blood plasma is indicative of acute illness as such, and that it is not associated with a special type of disease. In no case has a cause–effect relationship between increased PA-inhibitor levels and a certain disease been convincingly demonstrated, although at least in the case of deep venous thrombosis PA-inhibitory activity might have some prognostic value.89

In normal human blood at least two pools of PA-inhibitory activity are present.81 One pool is the (platelet-poor) plasma pool that shows a very rapid turnover and for which the normal values show a very large interindividual variation ranging from 0.0 to 1.3 nmol/L. The other pool is the platelet PA-inhibitor pool that probably shows a turnover of the order of magnitude of the turnover of platelets themselves (half-life three to four days) and for which the normal values show a much smaller range (mean: 6.7 x 10⁻¹⁴ mole/platelet; SD = 3.0 x 10⁻¹⁴).20 It can be calculated that in a given volume of blood the PA-inhibitory activity in the platelets is about four times higher than in the plasma.23 The platelet PA-inhibitory activity is probably present in the α-granules21,22 and is indistinguishable from PAI-1 in endothelial cells.23

During coagulation, the PA-inhibitor derived from platelets may play a very important role in protecting the blood clot against premature lysis. The high concentration of activated platelets in a blood clot may yield a local PA-inhibitor concentration that is several orders of magnitude higher than the value in plasma and would prevent too-sudden lysis. Instability of the PA-inhibitor at 37°C (in vitro half-life about two hours) and inactivation by activated
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protein C and thrombin may result in a gradual disappear-
ance of the inhibitor from the clot. Subsequent diffusion of
PA into the clot may result in clot lysis. Plasma PA-
inhibitory activity might serve in systemic PA-activity con-
trolling, preventing the unwanted action of PA under resting
conditions.

The role PA-inhibitors play in thrombolytic therapy with
PA remains to be established. A simple calculation shows
that in order to maintain a steady-state concentration of
PA-inhibitor of 1.0 nmol/L with a hypothetical half-life of
ten minutes in man, a rate of synthesis of 0.45 mg/hr is
required. This is far less than the amount of t-PA (up to 60
mg/hr) that is administered by intravenous injection as
thrombolytic therapy to patients with myocardial infarc-
tion. This amount of PA-inhibitor as such is probably not
a major factor in the success of thrombolytic therapy. On
the other hand, since data on PA-inhibitors during thrombolytic
therapy are presently lacking, conclusions cannot be drawn.

ACKNOWLEDGMENT

Drs E.J.P. Brommer, J.J. Emeis, V.W.M. van Hinsbergh, T.
Kooistra and J.H. Verheijen from our institute, who are all involved
in studies on PA-inhibitors, are acknowledged for support in writing
this manuscript.

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Plasminogen activator inhibitors

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