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The Role of Fibrinolytic Factors in Ischaemia

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Summary

The fibrinolytic system is an enzymatic cascade system whose activation leads to formation of a trypsin-like serine protease, plasmin, which splits insoluble fibrin into soluble degradation products. It is believed that the main function of fibrinolysis is defence against thrombotic occlusion of vessels and dissolution of thrombi once they are formed (thrombolysis).

The authors review the recent literature providing evidence that fibrinolysis plays a role in the pathogenesis of vascular occlusions. From earlier studies based on global assay methods it is known that fibrinolysis is depressed in patients with vascular occlusions. Selective assay methods show that almost invariably the fibrinolytic activity of these patients is depressed either following increased levels of fibrinolytic inhibitors (mainly plasminogen activator inhibitor 1 or PAI-1) and/or decreased levels of a plasminogen activator (tissue plasminogen activator or t-PA). In a few cases the molecule of plasminogen shows a conformational abnormality making it less susceptible to conversion to plasmin.

In the last decade numerous studies have been published showing a connection between a depressed fibrinolysis and venous thrombosis. In patients with coronary artery occlusion fibrinolysis is depressed mainly because of increased levels of PAI-1. Hypertriglyceridaemia seems to aggravate the defective fibrinolysis. There is also evidence of a decreased fibrinolysis in patients with peripheral ischaemic diseases.

A depressed fibrinolysis has also been documented in states predisposing to vascular occlusions. Thus lwo levels of t-PA/increased levels of PAI-1 have been found in obesity, diabetes mellitus, postoperative states, SLE, malignancies, and miscellaneous diseases often complicated with thrombosis such as Behçet's syndrome. In pregnancy fibrinolysis is depressed because of the presence in blood of PIA-2, an inhibitor of plasminogen activators secreted by the placenta.

The Fibrinolytic System

The fibrinolytic system is an enzymatic cascade system whose activation leads to formation of a trypsin-like serine protease, plasmin, which is capable of degrading fibrin as well as fibrinogen, factor V and VIII. It is believed that the main function of fibrinolysis is defence against thrombotic occlusion of vessels, dissolution of thrombi once they are formed (thrombolysis) and resolution of clots and fibrinous exudates occurring in various parts of the body.

Activators of fibrinolysis

A simplified scheme of the fibrinolytic system in man is shown in Figure 1.

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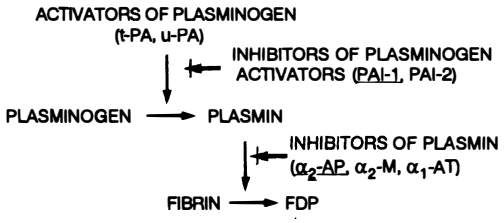

Fig. 1. *A simplified scheme of the fibrinolytic system.*

Plasmin splits fibrin into soluble fragments (fibrin degradation products—FDP) of different size. Plasmin results from activation of the proenzyme plasminogen, a β_2-glycoprotein with molecular weight of about 90 kD[1] which is synthetised in the liver.[2] It tends to be adsorbed to fibrin, the site at which the bulk of plasminogen activation occurs.

Circulating blood contains two types of plasminogen activators: tissue type activator (t-PA) and urinary activator or urokinase (u-PA). Both activators may be present in native single chain forms: weakly active sc t-PA[3] with a molecular weight of 60 kD, and sc u-PA (prourokinase) with a molecular weight of ~54 kD which is devoided of enzymatic activity.[4] An important functional difference between the two activators is that t-PA binds to fibrin which it needs to activate plasminogen while u-PA does not bind to fibrin and is capable of activating plasminogen in absence of fibrin. During activation of fibrinolysis both native forms are converted into the active two chain t-PA and u-PA (tc t-PA and tc u-PA).

T-PA is produced and stored in the endothelium of certain blood vessels where it can be demonstrated histochemically.[5] From the vascular endothelium t-PA is continously released into the circulation such release being enhanced by a variety of stimuli notably venous stasis[6] and physical exercise.[7] The concentration of t-PA antigen in plasma is low, about 5 μg/L. It is believed that t-PA plays the central role in maintaining the patency of the vascular tree by dissolving obstructing fibrin deposits or promoting the lysis of occluding thrombi.

U-PA is produced mainly by the kidney and excreted with the urine. Its main role is probably that of maintaining the urinary excretion pathways free from obstructing fibrin. Plasma contains minute amounts of u-PA mainly sc u-PA.[8] A variety of other cells such as malignant cells[9] and corneal epithelium[10] have been shown to produce u-PA.

The fibrinolytic system can be activated by kallikrein as well as by F.XII of coagulation (intrinsic activation system).[11,12] The pathophysiological role—if any—of the intrinsic activation system is not clarified.

Regulation of fibrinolysis. Fibrinolytic inhibitors

Since plasmin is capable of degrading proteins other than plasmin it is necessary to confine its action to its primary substrate i.e. fibrin. Furthermore the effectiveness of the fibrinolytic system needs constant regulation since a too pronounced activity leads to a haemorrhagic diathesis, while a depressed activity leads to thrombosis. The mechanisms regulating fibrinolysis have been the object of comprehensive reviews.[13–17]

While circulating in blood as free enzymes the activity of t-PA is weak. When fibrin is formed, plasminogen and t-PA are bound to fibrin. Fibrin bound t-PA increases 200 times its cathalytic activity and rapidly converts into plasmin the fibrin bound plasminogen. The result is a local fibrinolysis. Plasmin also converts the inactive sc u-PA into active tc u-PA which takes part in the dissolution of fibrin. However, the role played by u-PA in fibrin dissolution inside the vascular tree is probably ancillary.

The fibrinolytic process is restrained at two different levels by two classes of inhibitory agents present in plasma: the inhibitors of plasminogen activators,[18] and the inhibitors of plasmin. The main plasminogen activator inhibitor (PAI-1) is contained in the vascular endothelium and in the platelet alpha granules; it immediately binds t-PA and u-PA. In normal conditions it binds 95% of the circulating t-PA forming a complex with molecular weight of 110 kD.[7] Changes in PAI-1 plasma levels rather than changes in t-PA have been recently related to diurnal variations of the fibrinolytic activity.[19] PAI-2 has probably a secondary importance being secreted by placenta and being present only in plasma of pregnant women. However, PAI-2 has recently been found in the plasma of some men and non-pregnant women.[20]

In addition to its anticoagulant activity,

activated protein C (APC) stimulates fibrinolysis both *in vitro* and *in vivo*[21,22] by binding PAI-1 thus acting as an 'inhibitor of inhibitor'.[23] A similar action as protein S which acts as a cofactor of APC.[24]

The primary inhibitor of plasmin, α_2-antiplasmin (α_2-AP)[25] rapidly forms a complex with circulating plasmin. In case of massive formation of plasmin—as during thrombolytic treatment with streptokinase or in disseminated intravascular coagulation—an exhaustion of available α_2-AP occurs. The excess of plasmin is then complexed by α_2-macroglobulin which functions as a reserve ('second defence line') inhibitor of plasmin.[26] A_2-AP inhibits fibrinolysis also by preventing adsorption of plasminogen to fibrin, an essential step of physiological fibrinolysis.

C1 inhibitor is known to activate components of the complement C1s and C1r; it also inhibits clotting factor XIIa, XIa and kallikrein. Furthermore it reacts with plasmin and with t-PA although at such low rates that its significance as inhibitor of fibrinolysis is uncertain.[27]

The balance between the profibrinolytic and antifibrinolitic activity is regulated by the synthesis of these agents and by their release into circulation. Synthesis and release have been found to be mediated by a number of substances such as thrombin, histamin, epinephrine.[28] Another mechanism of regulation is the presence of binding sites for plasminogen, t-PA u-PA[29,30] on cellular membranes.

Clinical significance of fibrinolysis. Possible role in the pathogenesis of vascular occlusions

In the mid-50s there was enough knowledge on the fibrinolytic system to allow Astrup to present a scheme of fibrinolysis which was similar to the present one,[31] the only significant difference being that inhibitors of plasminogen activators were not reported. A number of functions have been attributed to the fibrinolytic system.

Fibrin deposits which may form within the vascular lumen are believed to be dissolved by an intact fibrinolytic system before they grow enough to threaten the patency of the vessel.[32] A corollary to the antithrombotic action of the fibrinolytic system is that administration of purified fibrinolytic enzymes brings about dissolution of occluding thrombi (therapeutic thrombolysis).

In inflammation and trauma fibrin is usually formed. During the healing process fibrin, which may act as matrix for neoformed vessels; is gradually broken down by the systemic and local fibrinolysis. A timely dissolution of fibrin is important to avoid bleeding or scarring.[31]

The role of fibrinolysis in tumour growth is unclear. Tumoural cells secrete u-PA[9] and it is generally known that certain tumours are surrounded by a wall of fibrin which may have a containment action but which may also act as a matrix for vascular proliferation.

Activators of fibrinolysis, mainly u-PA, have been found in disparate areas of the body such as kidney, prostate, cornea, pleura, aqueous humour.[33] Their function is probably that of maintaining the patency of small ducts and preventing the development of adherence between surfaces.

The most manifest clinical significance of fibrinolysis however, is its action of preventing vascular occlusion by thrombi. A corollary of such action is that a depressed fibrinolysis promotes thrombosis. To verify this hypothesis numerous studies have been done with the aim of detecting a decreased fibrinolysis in patients suffering from vascular occlusions of various type or presenting conditions predisposing to vascular occlusion.

Fibrinolysis and Vascular Occlusions

The studies directed towards establishing a link between vascular occlusion and depressed fibrinolysis can be divided in two groups, i.e. those investigating the fibrinolytic system in patients actually suffering from vascular occlusions and those dealing with the fibrinolytic system in conditions predisposing to vascular occlusions.

A. The fibrinolytic system of patients in whom vascular occlusion is the primary disease

1. *Venous thrombosis*

The first unequivocal report linking thrombosis with depressed fibrinolysis was published in 1961 by Nilsson and associates.[34] These authors described a young patient with

severe and widespread venous thrombosis who showed a strongly increased plasma level of an inhibitor of plasminogen activation. The inhibitor was most likely PAI-1, at that time not yet identified. Later the same author described four more patients including two uniovular twins affected by recurrent severe thrombosis since childhood with a high blood content of inhibitor of plasminogen activation.[35] Histochemistry of vein specimens obtained by biopsy from patients with venous thrombosis showed a decreased plasminogen activator activity of the vein wall.[36] Increased levels of fibrinolytic inhibitor was found in the plasma of a patient affected by retinal vein occlusion in both eyes.[37]

In a large series of patients with idiopathic venous thrombosis it was found that a large number of these patients had a defective fibrinolysis in the blood and/or vein walls.[38] The methods used were functional i.e. determination of the spontaneous fibrinolytic activity of plasma and the activity following venous stasis, as well as a histochemical method to assess the activity in the wall of vein specimens obtained by biopsy. These finding were confirmed by subsequent reports.[43]

Progress in the 80s led to the discovery and characterisation of PAI-1, review in[18] the fast acting inhibitor of t-PA. It was found that PAI-1 masked the fibrinolytic response to venous stasis.[44] Two mechanisms of defective fibrinolysis in thrombosis patients were identified i.e. low levels of t-PA or increased concentration of PAI-1.[45–47]

Of special interest is the occurrence of either type of defective fibrinolysis associated with recurrent thrombosis in members of the same family.[42,43,48–51] The defect seems to be inherited according to an autosomal dominant mode with high penetrance. Nilsson and Tengborn[49] consider it odd that an inherited disorder should be due to an increased synthesis of inhibitor and hypothetised the presence of an abnormal inhibitor with increased affinity for t-PA.

In some cases recurrent venous thrombosis may be associated with the presence of an abnormal plasminogen molecule.[52–54] However, the associated defective plasminogen-thrombosis seems weak considering that family members of the patients reported had a decreased plasminogen activity (down to 5–10% of the normal) and did not show thrombosis. A normal plasminogen molecule but in low amounts was also found to be associated with thrombosis.[55]

Hereditary low levels of protein C[56] and protein S[57] are accompanied by an increased incidence of venous thrombosis. However, because these two proteins connected mainly with inhibition of coagulation it is uncertain whether the supposed protecting action against thrombosis is mainly due to their anticoagulant action rather than to their profibrinolytic activity.

2. *Coronary artery occlusion*

In the last decade endoscopic studies have shown that thrombosis is not a sequel to myocardial infarction (MI) as previously supposed, but the precipitating factor in MI and unstable angina.[58,59] This evidence, together with the favourable results obtained with modern thrombolytic therapy,[60] attracted new interest on the fibrinolytic system in patients with coronary artery disease. The results of earlier studies using only functional methods of assessment suggested decreased fibrinolytic activity in these patients.[61–63] Recent results[64–66] provide evidence that the reduced fibrinolysis is mainly due to increased plasma levels of PAI-1, and in younger patients also to defective t-PA release from the vessels.[65] Depressed fibrinolysis seems also to predispose to reinfarction.[66] Interestingly, numerous known risk factors for MI such as cigarette smoking,[67] hyperlipoproteinaemia,[68,69] obesity (see below) are associated with decreased fibrinolytic activity. In particular, a positive correlation between PAI-1 levels and plasma triglycerides has been found.[64] However, a recent study,[70] while confirming the finding that PAI-1 activity is positively correlated with levels of triglycerides, failed to observe either increased PAI-1 or decreased t-PA in a group of 65 men with angiographically documented coronary artery disease. Kirschstein *et al.*[71] found that restenosis after percutaneous transluminal coronary angioplasty was significantly more frequent in patients who devloped lower fibrinolytic activity and released lesser amount of t-PA following venous stasis.

Depressed fibrinolysis has been reported also in ischaemic cerebrovascular diseases.[72,73]

3. *Peripheral schaemic diseases*
According to a recent report there is an association between deficient release of t-PA following venous stasis and occlusive arterial disease of the upper limbs.[74] An abnormal plasminogen molecule in patients with upper extremity ischaemia has also been reported.[75] In a large series of patients with peripheral vascular diseases both the resting fibrinolytic activity of plasma and the activity increase following venous stasis were significantly lower in the patient group than in controls.[76] No information is available on changes, if any, in the levels of PAI-1. Histochemical evaluation of the plasminogen activator activity in leg arteries of patients undergoing below-knee amputation revealed an abnormally low activity.[77] However, in collateral arteries plasminogen activator activity was as high as that of arteries in other parts of the body, a result suggesting that atherosclerosis is not accompanied by a general suppression of plasminogen activator activity in the arterial vascular tree. Experimental ischaemia has been found to decrease the fibrinolytic activity of the femoral artery of rat.[78]

B. The Fibrinolytic System in Conditions Predisposing to Vascular Occlusions

1. *Pregnancy*
It is known that pregnancy is a predisposing factor to thrombosis. The fibrinolytic system in pregnant women becomes increasingly depressed during pregnancy,[79] reponds poorly to venous stasis[80] and rapidly reverts to normal values after delivery following placenta separation.[81] Placenta is rich in PAI-1[82] and PAI-2.[83] These inhibitors pass into the circulation[84,85] leading to a depressed fibrinolytic activity.

2. *Metabolic disorders*
Human obesity is affected by a higher prevalence of arterial and venous thrombosis.[86] There are several reports showing that obese subjects have a depressed fibrinolysis as shown by a low spontaneous plasma fibrinolytic activity and defective fibrinolytic response to venous stasis.[87–89] Increased levels of inhibitors of plasminogen activator has been suggested to be behind the depression of fibrinolysis.[87,88] Interestingly, a positive correlation has been found between the levels of serum triglycerides and PAI-1 activity.[88] Weight reduction has been found to revert the fibrinolytic defect in obese subjects[90] while physical exercise augments the fibrinolytic response to venous occlusion in healthy adults.[91] There are numerous reports suggesting that lipaemia inhibits fibrinolysis.[92] Recently it has been found that lipoprotein, an independent risk factor for ischaemic heart disease, binds to the plasminogen receptors on endothelial cells thereby hindering the mechanism of thrombolysis.[93] No reports are available connecting the depressed fibrinolysis in obese subjects and the occurrence of thrombosis.

3. *Post-operative states*
Like trauma,[94,95] surgery has been reported to produce a pronounced depression of fibrinolysis.[96–98] If fibrinolysis is already depressed, the consequence may be a postoperative venous thrombosis. There are several studies on the fibrinolytic system in patients before surgery in order to evaluate the risk of postoperative thrombotic complications.[99–104] These studies, which are based on functional assay methods, report a direct relationship between low pre-operative fibrinolysis and an increased risk of developing thrombosis after surgery. More recent studies show that the depressed fibrinolysis observed before and in connection with surgery is largey due to increase in the plasma levels of PAI-1.[105–109]

4. *Systemic lupus erythematosus (SLE)*
Patients with autoimmune diseases (SLE, rheumatoid arthritis, scleroderma) are prone to venous and arterial thrombosis.[110] Such risk has been found to be related to an acquired autoantibody termed lupus anticoagulant or LA which is present in a moderate (10–15%) percentage of these patients.[82] LA consists of IgG or IgM antibodies against phospholipids which *in vivo* act as a thrombogenic factor despite their *in vitro* anticoagulant activity.[111] Patients with SLE tend to have a depressed spontaneous fibrinolytic activity of the blood and to respond poorly to fibrinolytic stimuli

such as venous stasis.[112–114] Defective fibrinolysis seems to correlate with the severity of the disease since it is absent in patients with mild forms of SLE.[115] The reason for depressed fibrinolytic activity seems mainly to be in increased levels of inhibitors of plasminogen activation.[114] Concomitant increased von Willebrand factor levels seem to indicate an endothelial cell dysfunction in patients with lupus anticoagulant.[114] However a recent report failed to show that patients with SLE and thrombosis have a fibrinolysis lower than controls.[116]

5. *Malignancies*

The thrombotic tendency generally observed in malignant diseases has been attributed to the release of thromboplastic substances from the tumour.[117] However, tumoural cells are known to produce fibrinolytic agents. For example *in vitro* cultures of carcinoma of the ovary have been found to produce an agent immunologically identical to u-PA[118] while melanoma cells produce an activator indifferentiable from t-PA.[119] Tendency to thrombosis notwithstanding, the presence of tumoural plasminogen activator may be explained by recent studies showing that patients with malignancy have an increased plasma levels of t-PA inhibitor,[120,121] a characteristic which is shared by patients with idiopathic venous thrombosis (see above).

6. *Miscellaneous conditions*

In Behçet's syndrome one third of the patients develop venous thrombosis.[122] These patients have been found to have a depressed blood fibrinolysis[123,124] and to release low amounts of plasminogen activator following vasogenic stimuli as injection of DDAVP, a vasopressin analogue.[123]

In 12 cases of thrombotic thrombocytopenic purpura plasminogen activator activity was found to be unmeasurably low but the levels of t-PA antigen were normal.[125] The finding could be explained by the presence in all 12 cases examined of an inhibitor directed to t-PA and u-PA. Low levels of protein C antigen presumably had a contributory action to the decreased activity.

Oral contraceptives are known to be associated with an increased risk for thromboembolism and women taking p-pills have been found to have an impaired response to fibrinolytic stimuli such as venous stasis.[126,127] However, in some women the depression of fibrinolysis is still present one year after cessation of p-pill intake, a fact suggesting a preexistent depression of fibrinolysis as previously suspected in these patients.[128]

Comment

While our knowledge about the fibrinolytic system has increased in the last few decades, our understanding of its main role in pathophysiology has remained at the stage of an assumption formulated in the mid 1950s, i.e. that fibrinolysis prevents thrombotic occlusion of blood vessels and promotes vascular recanalisation.[129] The persisting uncertainty depends on the fact that such a role is very difficult to prove. The pathogenesis of thrombosis is widely multifactorial and therefore notoriously elusive. And, as regards the factor haemostasis, thrombotic occlusions have been linked not only to depressed fibrinolysis but also to platelet hyperaggregability, deficiency in antithrombin III, increased levels of fibrinogen, coagulation factor V, VII, VIII,[130] deficiency of protein C or of its cofactor protein S.[131] Finally, formation or dissolution fibrin in the organism results from the interplay of two complex systems, coagulation and fibrinolysis, each involving a vast number of activators and inhibitors. Such systems are efficiently buffered and do not usually decompensate following the decrease of one or more components. This situation, unlike the action of a defective enzyme on a given metabolic pathway, makes the consequence of fibrinolytic disorders especially arduous to identify.

The assumed role of fibrinolysis in the pathogenesis of other changes which are far more time consuming than thrombosis such as arteriosclerosis may well remain impossible to prove. Astrup's hypothesis of an equilibrium between fibrin formation and fibrinolysis prevailing in the whole vascular tree[32] however appealing to our 'physiological common sense' is probably destined to remain at the stage of hypothesis for the foreseeable future.

A disturbing point is what one may call the 'bias of the positive result'. While embarking upon a study on fibrinolysis and vascular

occlusion it is unavoidable for the investigator to entertain a certain hope that a connection between decreased fibrinolysis and thrombosis or tendency to thrombosis is going to be found. Even if such expectation does not, as it should not, influence the results it may well dissuade the continuation of the study, or discourage publication if negative results are obtained. In this way the reviewer, faced by an unbalanced body of evidence, is likely to add his voice to an artificial consensus.

Having said that, one has to underline that, while not proven, the antithrombotic role of fibrinolysis is suggested by an impressive amount of evidence. First of all the location of t-PA in the endothelium of blood vessels, i.e. the most suitable site for counteracting thrombus formation and growth. Histochemistry provides a dramatic evidence of the fibrin-dissolving power of the vascular endothelium: one single endothelial cell contains sufficient t-PA rapidly to produce a gap in a 70 μm thick fibrin film large enough to be visible to the naked eye.[132] Faced by such a conspicuous action *in vitro* it seems unavoidable to attribute to the vascular endothelium a significant fibrinolytic (thrombolytic) function *in vivo* also. Recent clinical studies on patients with fresh coronary occlusion[133] document angiographically that i.v. administration of t-PA has a thrombolytic effect. Some clinical cases are singularly convincing. For example, it is difficult not to connect two unusual conditions, i.e. widespread thrombosis in young subjects and high plasma levels of fibrinolytic inhibitors.[21,22] Indirect evidence of the antithrombotic role of plasminogen activators is provided by numerous clinical observations that increased blood levels of t-PA/u-PA is accompanied by the presence of fibrin degradation products (FDP) in plasma[134] or the occurrence of haemorrhages.[135]

It seems reasonable to expect that an increased knowledge about fibrinolysis is going to improve our ability of preventing thrombosis and inducing thrombolysis.

Key words: Fibrinolytic inhibitors, Fibrinolysis, Ischemia, Plasminogen activators, Thrombosis.

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