Plasmin

Plasmin is a serine protease that cleaves cross-linked fibrin to produce fibrin degradation products, which are easily swept away and degraded in flowing blood.

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Related terms:

Protease, Fibrinogen, Thrombin, Matrix Metalloproteinase, Lysozyme, Tissue Plasminogen Activator, Urokinase, Plasminogen Activator, Nested Gene, Fibrinolysis

Plasmin

Francis J. Castellino, in
Handbook of Proteolytic Enzymes (Third Edition), 2013

Activity and Specificity

Plasmin catalyzes cleavages of Lys↓Xaa and Arg↓X bonds, with a specificity similar to that of trypsin. However, plasmin is a much less efficient enzyme than trypsin, and cleaves only some of these bonds in proteins. Of the simple amino acid substrates, esters and amides of arginine and lysine are cleaved with relative rates affected by the inherent susceptibility of the leaving group to hydrolysis. With these substrates, potentiometric and colorimetric assays were developed [9]. More modern plasmin assays with small substrates, such as peptides that contain C-terminal lysine and arginine amides or esters, take advantage of

p-nitrophenolate and *p*-nitroanilide leaving groups. These are assayed by the visible absorbancy (405 nm) of the released moiety. A comprehensive list of kinetic properties of synthetic substrates for plasmin has been published [10,11]. Similarly, amide- and ester-based synthetic substrates possessing a variety of fluorescent leaving groups have been designed to provide assays for plasmin with much higher sensitivities [10,12]. Single-turnover substrates that are derivatives of *p*-nitrophenylguanidinobenzoate [13] or 4-methylumbelliferylguanidinobenzoate [14] are very effective spectrophotometric or fluorometric titrants of plasmin [15,16]. A sensitive electrochemical assay for plasmin has been developed using a ferrocenyl peptide substrate with a k_{cat}/K_m value of 0.063 $\mu M^{-1} s^{-1}$ [17].

A wide variety of proteins are cleaved by plasmin at a very limited number of Arg-Xaa and Lys-Xaa bonds (*vide infr*a). Plasmin assays based on hydrolysis of casein [18] and fibrin [19] have been established. Preferences for the S1 to S4 substrate binding sites of plasmin have been determined using a combinatorial library of fluorogenic peptide substrates [20], and the S3 and S3′ sites using a combinatorial library of synthetic inhibitors [21]. A preference for aromatic hydrophobic residues in P2 was shown.

Most inhibitors of trypsin also inhibit plasmin, as do general serine protease inhibitors. DFP and Tos-Lys-CH_2Cl are irreversible inhibitors [22,23], and benzamidine [24] and its derivatives [25,26], as well as other aromatic amidines [27] and tetra-amidines [28], function as competitive, reversible inhibitors of plasmin. Leupeptin (R-Leu-Leu-argininal), and its synthetic analogs [29], in addition to naturally occurring fungal derivatives, R-Val-Val-argininal, R-Ile-Ile-argininal and R-Thr-Thr-argininal, are also excellent competitive inhibitors of plasmin [30].

Among the protein inhibitors, the Kunitz-type, serpin, soybean and limabean trypsin inhibitors inactivate the various molecular forms of plasmin [31–34]. α_2-Macroglobulin forms stoichiometric complexes with plasmin and inhibits access to the active site of only large molecular mass

substrates and inhibitors [35]. The physiologically relevant, fast-acting inhibitor of plasmin in plasma is α_2-antiplasmin [36]. Aprotinin (commercially known as Trasylol) is widely used during surgery to prevent bleeding, but can lead to problems such as myocardial infarction, vein graft hypercoagulation, and renal failure, and alternative, more selective inhibitors of plasmin have been sought, of which the most potent is Lys-Met(sulfone)-Tyr-Arg-H, which inhibits plasmin with a K_i of 3.1 nM [37].

The different molecular forms of plasmin interact with the same substrates and inhibitors, but to different extents [11]. A major difference is noted, in comparison to plasmin, in the enzymic specificity of the streptokinase–plasmin complex. While the activity of plasmin on small synthetic substrates is largely unaffected in the complex, the nonspecific protease activity is dramatically reduced. Importantly, plasmin alone does not catalyze activation of plasminogen, but the streptokinase–plasmin complex, although possessing diminished general proteolytic activity, serves as a very efficient plasminogen activator [38].

Effects of high-pressure homogenization on enzyme activity in milk and dairy products

Essam Hebishy, ... Antonio-Jose Trujillo, in
Effect of High-Pressure Technologies on Enzymes, 2023

8.4.1.4.1.1 Plasmin in milk

Plasmin (PL), a serine proteinase enzyme (48,000 Da), is the major indigenous proteinase in milk present at a level of 0.3 mg/L.[85] It is the active part of a complex enzyme system. In raw bovine milk, the PL zymogen is called plasminogen (PLG), which is 2–30 times higher in

concentration than PL.[86] Two PLG activators, urokinase-type plasmin activators (PA) (uPA) and tissue-type PA (tPA) PLG, are responsible for PLG activation into PL. There are also inhibitors that regulate the activity of PL and PLG activators, such as α2-antiplasmin and plasminogen activator inhibitors.[86,87] The level of PL in milk can vary and depends on environmental factors, such as stage of lactation and somatic cell count.[88] PL's optimum pH is 7.5, and the optimum temperature is approximately 37°C.

Agricultural and Related Biotechnologies

H.S. Garcia, ... C.G. HillJr., in
Comprehensive Biotechnology (Second Edition), 2011

4.47.2.3 Plasmin (EC 3.4.21.7)

Plasmin (PL) is an alkaline serine proteinase that hydrolyzes α_{s1}-, α_{s2}-, and β-casein. The PL proteolytic system of milk consists of PL, plasminogen, plasminogen activators (PAs), PA inhibitors, and PL inhibitors. In bovine milk, PL is secreted as plasminogen, a protein consisting of 786 amino acid residues. PL has a molecular weight of 88, 092 Da and is activated in milk by the hydrolysis of Arg557–Ile558. In milk, PL exists in both active and inactive forms, each of which is associated with casein micelles. This enzyme has an optimum activity at pH 7.5 and 37 °C, and a marked affinity for lysine and arginine residues. PL preferentially cleaves Lys X and Arg–X bonds. Increased PL activity occurs in milk at the end of lactation, in older cows, and in mastitic milk.

When present in either the casein or whey fractions of milk involved in cheese making, PL activity has a very significant impact on the quality of cheese (and also whey protein products). Increased levels of PL in the casein fraction would be beneficial for most cheeses. However, in order to

avoid thinning in some products to which caseinates are added, it may be desirable to release PL from the casein micelles when producing casein protein products such as sodium caseinate. Moreover, most applications of whey protein products require that there be little or no PL present in the whey. The PL contents of commercial whey protein concentrates range between 20.5 and 330 $\mu g g^{-1}$ of protein; the PL activity present in commercial whey protein isolates corresponds to only a small fraction of this number (between 2.0 and 2.9 $\mu g g^{-1}$ of protein). Increased PL levels in the whey fraction can cause protein breakdown in food products to which whey is added as an ingredient, thereby decreasing the quality of said product.

At times, proteolysis induced by PL is essential for flavor development and textural changes that occur during ripening of cheese, thereby enhancing the product quality. Reduced PL levels can cause delays in ripening and lead to reductions in flavor and texture quality. Under such circumstances, longer ripening times will be required with a concomitant increase in production costs. In the manufacture of cheese, uncontrolled proteolysis has a detrimental effect because of poor curd formation. PL and plasminogen in milk are heat resistant and survive most UHT (ultra high temperature) pasteurization treatments. Gelation is a common problem affecting the quality of ultra-pasteurized dairy products during storage for long periods. Several researchers have proposed that the PL system plays a key role in the deterioration process.

The most important substrate of PL in cheese is β-casein. This protein is hydrolyzed at three sites: Lys28–Lys29, Lys105–His106, and Lys107–Glu108; α_{s2}-casein is also very susceptible to PL action and its disappearance in cheese during ripening is related to the activity of this enzyme [10]. PL activity is most notorious in cheese varieties that are cooked at high temperatures (e.g., Swiss) because of the thermal stability of PL. Moreover, this enzyme plays a very important role in the proteolysis that occurs in mold-ripened and smear cheeses in which the pH increases during ripening [11, 12].

Enzymatic vitrectomy and pharmacologic vitreodynamics

David T. Goldenberg MD, Michael T. Trese MD, in
Retinal Pharmacotherapy, 2010

OUTCOMES

Plasmin and microplasmin are the most widely used agents for enzymatic vitrectomy. Multiple small case series have reported favorable results with APE as a surgical adjunct,[3–5,28,42–45] and clinical trials are currently under way with microplasmin.

APE and microplasmin may be most beneficial as a surgical adjunct in pediatric cases, whereby the vitreous is especially adherent to the retina and poses an increased risk of complications with mechanical separation. APE-assisted vitrectomy allows for easier peeling of the vitreous gel with a reduced risk of causing iatrogenic retinal breaks in cases of pediatric traumatic macular holes,[4] stage 5 retinopathy of prematurity,[44] congenital X-linked retinoschisis,[45] and other pediatric vitreoretinopathies.[43]

Plasmin enzyme has also shown promising results with adult vitreoretinal disorders. APE-assisted vitrectomy for stage 3 macular holes allows for easier removal of the posterior hyaloid, increased spontaneous PVD, and reduced operative time.[3] APE-assisted vitrectomy may also improve removal of the posterior hyaloid,[5,42] reduce surgical time,[42] and reduce iatrogenic retinal tears[42] in patients with diabetic tractional retinal detachments. Furthermore, patients with diabetic macular edema have shown improved visual acuity after APE-assisted vitrectomy but with mixed results regarding the resolution of edema.[5,28]

URL: https://www.sciencedirect.com/science/article/pii/B9781437706031000521

Pharmacology at Surgery

Christos Haritoglou, Anselm Kampik, in Retina (Fifth Edition), 2013

Plasmin

Plasmin was initially used by Verstraeten and coworkers to facilitate a PVD during vitrectomy in rabbit eyes. They found a positive effect but also mentioned a transient reduction of the b-wave amplitude in the electroretinogram as a potential adverse effect.[13] This study was followed by other experimental trials confirming the proteolytic activity of plasmin on the vitreoretinal junction. Autologous plasmin was then used in clinical case series investigating the effect of a single injection without vitrectomy as a treatment for refractory diffuse diabetic macular edema,[14] tractional diabetic macular edema[15] or macular edema associated with branch retinal vein occlusion.[16] The reduction of retinal thickness and improvement of visual acuity in these series supported an effectiveness of plasmin and the need for further trials. Autologous plasmin-assisted vitrectomy was performed for stage 3 macular holes, traumatic macular holes, diabetic macular edema and stage 5 retinopathy of prematurity[17–22] and all of these trials underlined the potential of plasmin to facilitate vitrectomy and its good safety profile.

Read full chapter

URL: https://www.sciencedirect.com/science/article/pii/B9781455707379001272

Agricultural and Related Biotechnologies

H.S. Garcia, ... C.G. HillJr., in Comprehensive Biotechnology (Third Edition), 2017

4.52.2.3 Plasmin (PL; E.C. 3.4.21.7)

Plasmin is an alkaline serine proteinase that hydrolyzes α_{s1}-casein, α_{s2}-

casein, and β-casein. The plasmin proteolytic system of milk consists of plasmin, plasminogen (PG), plasminogen activators (PA), plasminogen activator inhibitors (PAI) and plasmin inhibitors (PI). In bovine milk, plasmin is secreted as plasminogen, a protein consisting of 786 amino acid residues. PL has a molecular weight of 88,092 Da and is activated in milk by hydrolysis of Arg557–Ile558. In milk, plasmin exists in both active and inactive forms, each of which is associated with casein micelles. This enzyme has an optimum activity at pH 7.5 and 37°C, and a marked affinity for lysine and arginine residues. Plasmin preferentially cleaves Lys-X and Arg-X bonds. Increased plasmin activity occurs in milk at the end of lactation, in older cows, and in mastitic milk.

When present in either the casein or whey fractions of milk involved in cheese making, plasmin activity has a very significant impact on the quality of cheese (and also on the associated whey protein products). Increased levels of plasmin in the casein fraction would be beneficial for most cheeses. However, in order to avoid thinning in some products to which caseinates are added, it may be desirable to release plasmin from the casein micelles when producing casein protein products such as sodium caseinate. Moreover, most applications of whey protein products require that there be little or no plasmin present in the whey. The plasmin contents of commercial whey protein concentrates range between 20.5 and 330 μg/g of protein; the plasmin activity present in commercial whey protein isolates corresponds to only a small fraction of this number (between 2.0 and 2.9 μg/g of protein). Increased plasmin levels in the whey fraction can cause protein breakdown in food products to which whey is added as an ingredient, thereby decreasing the quality of said product.

Plasmin induced proteolysis can have either positive or negative effects on the texture and flavor of dairy products, depending on the extent of hydrolysis and the particular dairy product of interest. In cheeses, proteolysis is important in the development of the desired flavor profile and texture during ripening. Reduced plasmin levels can cause delays in

ripening and lead to reductions in the quality of both flavor and texture. Under such circumstances longer ripening times will be required with a concomitant increase in production costs. Plasmin activity is most deleterious in cheese varieties that are cooked at high temperatures (eg, Swiss) because of the thermal stability of plasmin. Uncontrolled proteolysis can then produce the detrimental effect of poor curd formation. This enzyme also plays a very important role in the proteolysis that occurs in mold-ripened and smears cheeses in which the pH increases during ripening [14,15]. Although the most important substrate of plasmin in cheese is β-casein, α_{s2}-casein is also very susceptible to reaction in the presence of plasmin. Its disappearance in cheese during ripening, is related to the activity of this enzyme [16–18].

Plasmin and plasminogen in milk are heat resistant and survive most UHT treatments. Consequently, in production of pasteurized milk and UHT milk, proteolysis can lead to undesired gelation of the product with adverse consequences for shelf life and flavor. There is an extensive body of literature dealing with enhancing or minimizing proteolysis associated with the activity of the components of the plasmin system in casein and whey products depending on the ultimate dairy product application of interest. The goal of the associated research effort is to reduce product costs while improving the quality of the dairy product. Ismail and Nielsen [15] have reviewed this problem in much more detail than can be presented here. Chavan *et al.* [16] have prepared an extensive review of these interrelations for UHT milk processing and the effects of plasmin activity on shelf life. Gelation of UHT milk during storage is a major factor that limits the shelf life of this product. Shelf life can be extended by deactivation of enzymes via one of several alternative routes. This article also treats several practical problems of interest to those involved in dairy processing operations.

Clinical Biochemistry of Blood Coagulation

D.E.G. Austen, in

Scientific Foundations of Biochemistry in Clinical Practice (Second Edition)

, 1994

Plasmin, Plasminogen and Antiplasmin

Plasmin is a proteolytic enzyme responsible for dissolving fibrin clots and plasminogen is its inactive precursor.[35] Plasminogen is a single-chain glycoprotein with a molecular weight of approximately 92 000, circulating in the blood at a concentration of about 75 μg/mL. As molecular contact of fibrin strands is limited to the nodular bodies, open channels are available for plasminogen and plasminogen activators to enter. There they both adsorb on to the fibrin and plasminogen is activated *in situ*.Plasmin is therefore produced where it is needed and where it is protected from attack by plasmin inhibitors. As fibrin dissolves, plasmin is released into the circulation and is rapidly consumed by the inhibitor.

Plasmin activators circulate in the blood at a low level but, following stress or exercise, the concentration markedly increases. The released material has a higher molecular weight of 67 000 compared to that of the circulating activator, which is of approximately 54 000. Active plasmin has a molecular weight of approximately 85 000 and is composed of two chains of 60 000 and 25 000. The major inhibitor of plasmin is α_2-antiplasmin, which circulates at a concentration of about 70 μg/mL and has a molecular weight of approximately 70 000. The next most important one is α_2-macroglobulin.

Normal Coagulation and Hemostasis

S. Chamarthy, in Pathobiology of Human Disease, 2014

Thrombin-activatable fibrinolysis inhibitor

Both plasmin and thrombin can activate TAFI and this reaction is accelerated by combination of thrombin and TM. TAFI is a proenzyme to a zinc-bound metalloprotease. It functions by removing lysine and arginine residues from fibrin and fibrin cleavage products. These residues form part of the protein important in conversion of plasminogen to plasmin, and removing them alters the binding site of plasminogen needed to form plasmin. As a result, fibrin clot increases in size and fibrinolysis is inhibited. The production of plasmin is decreased and there is reduced clot lysis.

Therapeutic Agents for Posterior Segment Vitrectomy Surgery

LUCIAN V. DEL PRIORE, ... TONGALP H. TEZEL, in Ocular Therapeutics, 2008

A Plasmin

Plasmin is an autologous serum protease that is a key component of the fibrinolysis cascade. Plasmin is a non-specific protease usually present in human serum, and it is responsible for degrading a variety of plasma proteins; its specific physiologic role is to degrade fibrin clots. Plasmin is created when plasminogen, its precursor, is released into the circulation and activated by tissue plasminogen activator (TPA), urokinase plasminogen activator (uPA), or streptokinase. The activity of plasmin can be inhibited by the presence of alpha 2-antiplasmin, a serine protease

inhibitor. Deficiency in plasmin may lead to thrombosis, as clots are not degraded adequately. Plasmin is not present in normal vitreous, but is present in the subretinal fluid of patients with rhegmatogenous retinal detachment; prior authors have speculated that the presence of plasmin may increase detachment of the retinal pigment epithelium from the inner aspects of Bruch's membrane and thus accelerate or increase the risk of proliferative vitreoretinopathy (Immonen *et al.*, 1989, 1988).

Several approaches have been used to induce posterior vitreous detachment with plasmin. Gandorfer *et al.* (2004) injected plasmin (1-2 U/100 microliters) into the vitreous of enucleated porcine eyes, and showed that eyes receiving plasmin had separation of the cortical vitreous from the internal limiting membrane with no structural changes in the retina, with the degree of separation depending on the concentration and duration of plasmin exposure (Gandorfer and Kampik, 2005). Plasmin has been injected into the vitreous cavity of rabbits *in vivo* and been shown to be vitreolytic without toxicity (Kim *et al.*, 2004). Intravitreal plasmin also induces a posterior vitreous detachment in human eyes *in vitro* after intravitreal injection (Li *et al.*, 2002). Prior workers have used TPA as a biological activator to convert plasminogen to plasmin *in vivo*; predominantly TPA has been used to lyse blood clots in this setting, but TPA has also been used to induce a posterior vitreous detachment with simultaneous addition of cryotherapy to break down the blood–retinal barrier and therefore allow plasminogen to move into the vitreous cavity (Hesse *et al.*, 1995, 2000). Hikichi *et al.* (1999) induced a posterior vitreous detachment with a combination of intravitreal injection of sulfur hexafluoride plus intravitreal plasmin injection to induce a posterior vitreous detachment; it is possible that either alone would have induced a posterior vitreous detachment in this experimental setting.

In the clinical setting we can envision several ways in which plasmin can be used to induce vitreous liquefaction followed by vitreous detachment. Autologous plasmin can be harvested from a patient's blood prior to surgery, purified, and then injected into the vitreous cavity (Asami *et al.*,

2004; Azzolini *et al.*, 2004). An affinity cartridge has been developed so that autologous plasminogen can be used for posterior vitreous detachment induction (Asami *et al.*, 2004; Azzolini *et al.*, 2004). The plasminogen is then converted to plasmin using streptokinase, which can then be used for surgical procedures. The method can be adapted to purify other blood components. Autologous plasmin enzyme has been demonstrated to assist with the production of posterior vitreous detachment in patients undergoing surgery for diabetic macular edema; the level of suction required during vitreous surgery to induce a posterior vitreous detachment was lower in the plasmin-treated versus control eyes (Asami *et al.*, 2004; Azzolini *et al.*, 2004). Plasmin has also been used as a surgical adjuvant for the closure of traumatic (Chow *et al.*, 1999) and pediatric macular holes (Margherio *et al.*, 1998). Autologous plasmin enzyme has been used during diabetic vitrectomy for macular edema, and been shown to create a posterior vitreous detachment in this setting and thereby facilitate surgery (Sakuma *et al.*, 2006, 2005a). A clinical trial of this agent is currently ongoing. Intravitreal injection of TPA coupled with cryotherapy has been demonstrated to be efficacious for this purpose (Hesse *et al.*, 1995, 2000).

Blood: blood clotting

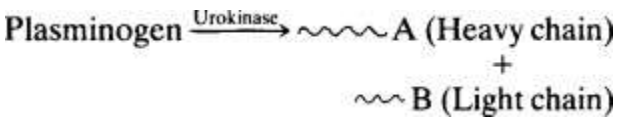
Eric D. Wills, in Biochemical Basis of Medicine, 1985

26.10 Fibrinolysis

Although the fibrin clot is resistant to the action of proteolytic enzymes, it is attacked by a special protease called ‘plasmin’. This enzyme does not occur in plasma but its precursor, plasminogen, occurs in the human and most animal plasmas at a total concentration of 200 μg/ml. The molecular weights of the plasminogens vary between 82 000 and 92 000. One group

of plasminogens contains glutamate as its terminal amino group whilst the other group contains lysine in this position. Multiple forms of plasminogen occur in each group and can be separated by electrophoresis.

Activation of plasminogen is analogous to the activation of trypsin or thrombin and has been detected in the blood, in many tissues, in saliva, and in the vascular epithelium. Activating enzymes, such as urokinase, have been isolated from urine, and streptokinase has been isolated from several bacteria. The mechanism of activation of plasminogen may vary with the activator, but it has been studied in detail for urokinase:



The split between Arg–Val residues in plasminogen causes the formation of a heavy A chain and a light B chain, the active site being located in the B chain.

In addition to a large group of plasminogen activators, many inhibitors are known. These fall into two groups: (*a*) those which inhibit plasminogen activation (antiactivators) and (*b*) those which inhibit plasmin (anti-plasmins). Anti-activators are less well defined than anti-plasmins but they occur naturally in the blood and are proteins of molecular weight 75 000–80 000 associated with the α_2 globulin fraction.

Five different plasma protease inhibitors acting as anti-plasmins have been purified. They form complexes with the enzyme proteins which are inactive. Platelets contain an antiplasmin factor and vitamin E (α-tocopherol) in physiological concentrations also possesses this activity. As a consequence of the presence of this wide spectrum of inhibitors, plasmin is not detectable in the plasma.

Plasmin tested *in vitro* is a relatively non-specific protease and the question arises as to why, *in vivo,* it has a special affinity for the fibrin clot. Although this problem has not been resolved, three possible explanations

have been advanced:

a. There is preferential absorption of plasminogen to the fibrin clot to allow proteolysis to occur subsequently
b. Plasmin is normally bound to anti-plasmins in plasma but that these dissociate when the complex is bound to the fibrin clot
c. Activators are selectively bound to the fibrin clot which activates the plasma as it becomes attached.

Hypothesis (*a*) involving plasminogen absorption is the most widely accepted.

The stages of the plasma degradation of fibrin are shown in *Fig.* 26.19. The first stage of proteolysis involves the removal of peptides with a molecular weight of about 40 000 from the carboxyl ends of the Aα chains leaving the residual Aa chain remnants bonded to intact Bβ and γ chains by S–S links. The group of products, of molecular weight 260 000–300 000 is called 'fragment X'.

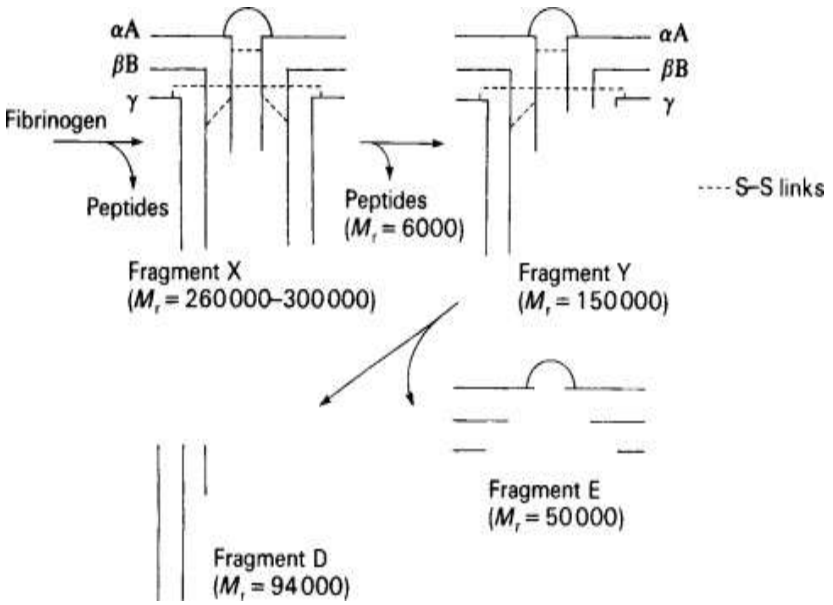


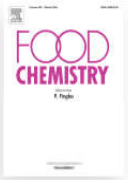
Fig. 26.19. Degradation of fibrin by plasma.

The next stage of cleavage involves the removal of peptides (mol. wt 6000) from the N-terminal ends of the Bβ chains, followed by the

asymmetrical splitting of a large fragment D (mol. wt 94 000) leaving fragment Y. Proteolysis of the Aa, Bβ and γ chains of fragment Y yield an additional fragment D and a smaller fragment E (mol. wt 50 000).

Although this scheme describes the main process of fibrinolysis, it should be noted that there are many details remaining to be resolved. For example, fragment X is not a single well-defined protein but a heterogeneous mixture with a range of molecular weight of 240 000–300 000. Furthermore many smaller peptides, of molecular weights 20 000–30 000 can often be detected during the course of fibrinolysis. Proteolytic digestion of cross-linked fibrin by plasmin also yields a dimer of fragment D and fragment E(*Fig.* 26.19).

Fibrinolysis is an important defence mechanism of the body against thrombosis. Fibrin deposited in thrombi is cross linked and this linking is an important rate-limiting factor in lysis. In view of the chemical importance of formation of thrombi in blood vessels, more research is therefore being devoted to the investigation of the process, for example by measurements of the rate of formation of the fragment D–dimer complex in the plasma by immunological assays.



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