Pharmacologic Vitreolysis with Tissue Plasminogen Activator

VI.C.

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Keywords
Vitreous • Pharmacologic vitreolysis • Tissue plasminogen activator (tPA) • Subretinal hemorrhage • Vitreous liquefaction • Posterior vitreous detachment

Key Concepts

1. In the presence of fibrin, tissue plasminogen activator transforms the circulating inactive proenzyme plasminogen into the active protease plasmin.
2. Tissue plasminogen activator was the first enzyme clinically used in ophthalmology for diseases of the posterior segment, available for clinical use through recombinant DNA technology.
3. Tissue plasminogen activator is able to induce posterior vitreous detachment, which provides benefits in the course of many other diseases of the posterior segment.

I. Introduction

In the late 1980s and early 1990s, it was assumed that vitrectomy is a perfect tool to handle most vitreoretinal diseases even in cases of vitreo-macular traction. However, vitrectomy surgery includes risks like retinal detachment, hemorrhages, cataract formation, and infections. To avoid these problems, there is a need for a pharmacologic approach called pharmacologic vitreolysis. The use of enzymes in ophthalmology has a long history, as some of these enzymes, like hyaluronidase [1] and collagenase [2], were investigated long before vitrectomy was introduced. Further investigations for liquefaction and posterior vitreous detachment were undertaken in the early 1990s with different types of enzymes.

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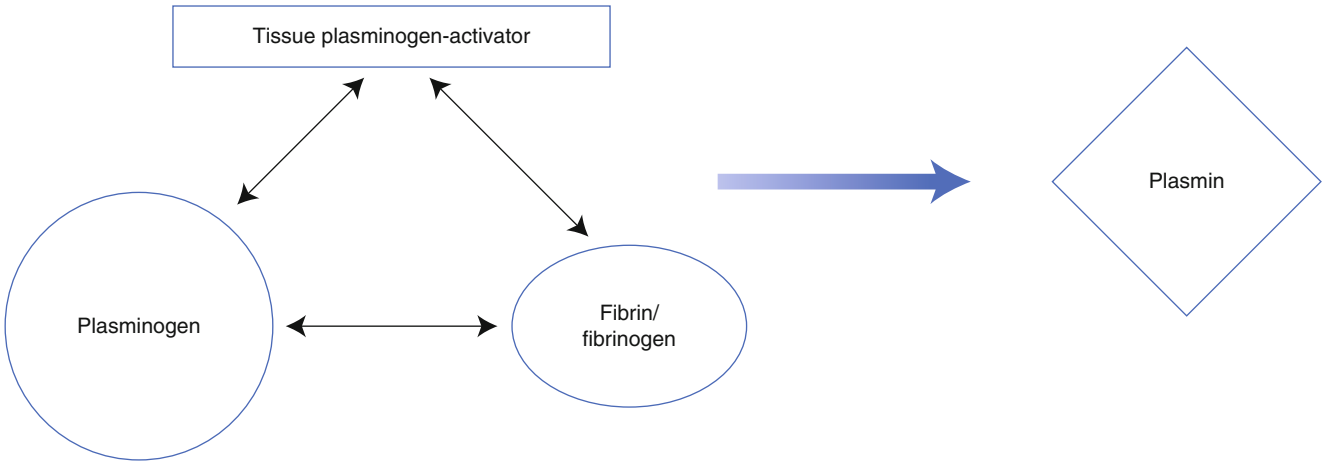

Figure VI.C-1 The fibrinolytic cascade. Protease plasmin is catalyzed in the presence of tissue plasminogen activator (*tPA*) and fibrin, forming a ternary complex. The presence of fibrin increases the enzymatic activity of tPA and thereby the proteolytic activity of plasmin

Streptokinase [3], hyaluronidase [4, 5], nattokinase [6], and chondroitinase [4, 7–9] were investigated but had significant side effects or insufficient clinical efficacy.

Verstraeten and colleagues first demonstrated in 1993 [10] that a posterior vitreous detachment in rabbit eyes could be achieved after intravitreal injection of plasmin. In 1999, Hikichi and coworkers [11] confirmed the finding of a complete PVD after injecting 1U plasmin and 0.5 cc SF6 gas into the vitreous of rabbits. However, for clinical use, plasmin must be prepared from autologous blood, a tricky and expensive laboratory technique.

In 1995 at the Vail Vitrectomy Meeting, Wilson Heriot [12] from Australia surprised all in attendance with a case series of four patients with submacular hemorrhages, which he treated successfully with an intravitreal injection of tissue plasmin activator (tPA) to liquefy the submacular blood clot and co-injection of SF6 gas to displace the hemorrhage out of the macular area through prone positioning of the patient. His exceptional results based on a minimally invasive procedure were confirmed by Hesse in 1997 [13]. This subject is extensively discussed in chapter V.A.1. AMD surgery.

II. Properties of Tissue Plasmin Activator

A. Biochemical

The main component of the fibrinolytic cascade is plasminogen, which circulates as an inactive proenzyme in the human blood (200 mg/L). Plasminogen activator, which is generated either in the human blood (intrinsic) or in the tissue (extrinsic), mediates the circulating proenzyme plasminogen into the fibrinolytic effective protease plasmin (Figure VI.C-1). tPA is fibrin specific that means tPA has a high affinity to fibrin. tPA, plasminogen, and fibrin form a ternary complex; thereby the catalytic efficiency of plasmin activation is increased three-fold. Plasmin is insufficiently produced in the presence of fibrinogen, which is the soluble precursor of fibrin. Plasmin itself is a trypsin-like serine protease, which activates the degradation of fibrin but also of fibronectin, laminin, and other peptides [14, 15]. Although plasmin is known as a key enzyme in blood clot lysis, it displays a broad-spectrum activity. It degrades extracellular matrix as well as fibrin and activates other proteinases such as prometalloproteinases (MMP-1, MMP-3, and MMP-9). Plasmin can also activate or release growth factors from the extracellular matrix including latent transforming growth factor (TGF-b), basic fibroblast growth factor (bFGF), and VEGF. This function supports cell movement, proliferation, inflammation, and invasive growth of cancer cells. Today tPA is available for clinical use through recombinant technology. It is also known by the names alteplase, reteplase, and tenecteplase, substances with FDA approval for the treatment of myocardial infarction, acute ischemic stroke, acute massive pulmonary embolism, and central venous access device occlusion. Desmoteplase, an additional recombinant tPA, is still under clinical investigation. All these activators have in common that their enzymatic activity increases up to the 100-fold in the presence of fibrin [16].

B. Methods of Generating Intravitreal tPA

An intravitreal injection of tPA is the most simple and effective technique to achieve high intraocular concentrations of the enzyme. Today ophthalmologists are experienced in this technique, but three decades earlier, most ophthalmic surgeons mistrusted intravitreal injections. Thus, tPA was given via intravenous route [17], transretinal route via placement onto the retinal surface during vitrectomy [18, 19], or via transscleral route by introduction into the choroid [20]. However, these alternative techniques resulted in incomplete

liquefaction of subretinal hemorrhage due to ineffective tissue levels of tPA (intravenous administration) or limited time and thereby incomplete clot lysis during vitrectomy [21].

Peyman generated tPA by injecting plasminogen and urokinase separately and allowing their interaction to create tPA. Studies [22] showed that this was nontoxic to the retina at plasminogen concentrations of 2.0 CU or less and could induce PVD in rabbits. Subsequent studies [23] showed that recombinant lysine-plasminogen and recombinant urokinase with the addition of an intravitreal injection of sulfur hexafluoride gas induced a PVD in 75 % of rabbits tested. To our knowledge, no human studies were ever undertaken.

C. Clearance of tPA

After intravitreal injection, the clearance of tPA depends on three factors: the presence of (1) fibrin, (2) vitreous, and (3) plasminogen activator inhibitors. Following intravitreal injection, the peak concentration of tPA in vitreous will be achieved after approximately 6 h [24]. Therefore, it is recommended that in cases of submacular hemorrhage tPA should be injected intravitreally as a first step and between 12 and 24 h later the gas to displace the liquefied blood clot should be introduced in a second step. A simultaneous injection of tPA and gas is possible and widely used, but prone position should be avoided in the first hours because the surface of the gas bubble may cover the subretinal hemorrhage, thereby preventing tPA from crossing the retina and entering the clot.

D. Toxicity of tPA

Toxic side effects after intravitreal tPA are well known. The cause of retinal damage is not the tPA protein itself but L-arginine, an added stabilizer of the formulation [18]. Pure tPA (50 µg intravitreal or 20 µg subretinal) has no toxic effect on the retina [13, 18]. One reported patient [13] received a high dose of 100 µg and developed a serous retinal detachment in the lower part of the eye, which recovered after one and a half months, leaving an irregular pigmentation in the area of the previously detached retina. The visual field recovered and the visual acuity was not affected, albeit limited by underlying AMD. Further reports confirmed that a safe intravitreal dose was 40–50 µg, with toxic side effects to the retina occurring with doses of 50 µg and more [25].

III. Ophthalmic Indications and Applications of tPA

In 1988 Williams et al. [26] were the first to report on three patients with intraocular fibrin formation after pars plana vitrectomy and their successful treatment with tPA, injected into the anterior chamber of the eye. Thereafter, tPA was mentioned as a standard treatment for anterior segment disorders like fibrin or fibrin membrane formation after cataract surgery [27], fibrin or blood-induced ocular hypertension after glaucoma surgery or keratoplasty [28, 29], and fibrin-induced blockage of a basal iridectomy after silicone oil surgery [30]. For the posterior segment inflammatory conditions after vitrectomy with fibrin formation or even with an endophthalmitis [31], tPA is a further option for treatment. With more knowledge about tPA in ophthalmology, these therapeutic options became standard, without being further mentioned in the ophthalmic literature. However, experimental studies to resolve vitreous hemorrhage with tPA failed [32], because of its less convincing therapeutic effect.

A. Submacular Hematoma

See chapter V.A.1. AMD surgery.

B. Induction of Posterior Vitreous Detachment (PVD)

A new application for tPA appeared in 1993 with the landmark paper of Verstraeten et al. [10] which demonstrated that as a protease, plasmin is able to split the extracellular matrix proteins fibronectin and laminin at the vitreoretinal interface, which normally glue the vitreous cortex to the retina. The consequence of this enzymatic effect of tPA leads to a dissolution of fibronectin and laminin, resulting in a posterior vitreous detachment (PVD). In 1995, after Heriot's presentation, Hesse et al. [33] published the first study about an enzymatically induced PVD in diabetic patients. With this idea of an easy method to create a pharmacologic PVD without or in combination with a vitrectomy, a new concept for pharmacologic treatment of vitreoretinal diseases without the demanding production of autologous plasmin became inaugurated, named pharmacologic vitreolysis by Sebag in 1998 [34]. Other reports [35, 36] with different indications described the benefit of intravitreal tPA and the induction of posterior vitreous detachment. In rabbits, a PVD was induced by combining cryopexy and intravitreal injection of tPA. The effect is based on plasminogen which enters the vitreous after breakdown of the blood-retinal barrier through cryopexy [37].

Knowing that depending on the amount of attendant fibrin, the half-life of tPA is between 5.8 and 11.8 h and that the generated peak for the active agent plasmin is about 6 h, it is recommended that for a striking effect of pharmacologic vitreolysis, tPA should be injected 24 h before a surgical intervention. This would guarantee a tPA effect, since Le Mer et al. [38] were not convinced by the pharmacologic

effect of tPA during vitrectomy in diabetic patients, injecting the agent only 15 min before the surgical intervention.

C. Proliferative Diabetic Vitreoretinopathy

In 1995, Hesse et al. [33] published the first study about pharmacologic vitreolysis induction of PVD in diabetic patients. The first clinical reports about autologous plasmin appeared later by Williams et al. [39] in the treatment of diabetic retinopathy. In both case series, they observed posterior vitreous detachment, which facilitated the surgical intervention [see chapter VI.D.1. Pharmacologic vitreolysis with plasmin: basic science experiments, VI.D.2. Pharmacologic vitreolysis with plasmin: clinical studies]. The encouraging results of Hesse et al. [33] and Hesse [40] in treating proliferative diabetic vitreoretinopathy (PDVR) with tPA, which facilitates vitrectomy, would justify further studies with tPA, to verify the effectiveness of pharmacologic PVD induction in comparison with other agents, like autologous plasmin, which is not easy to produce, or ocriplasmin which has been recently approved by the EU and FDA [41], but has not been applied yet to PDVR [see chapter VI.E.2. Pharmacologic vitreolysis with ocriplasmin: clinical studies].

With the knowledge that in diabetic patients, the posterior vitreous cortex plays an important role in the development of neovascularization into the vitreous, a PVD seems to be an effective treatment to prevent this pathology [see chapter III.L. Proliferative diabetic vitreo-retinopathy]. A thickened vitreoretinal interface and a thickened posterior vitreous cortex represent a metabolic barrier [see chapter IV.A. Vitreous physiology] that promotes proliferation of new retinal vessels into the attached posterior vitreous cortex that also serves as a scaffold for the proliferating vessels. Therefore, in cases of severe diabetic retinopathy that are not yet proliferative, panretinal photocoagulation is routinely employed throughout the world. However, the beneficial effect of panretinal photocoagulation is not understood, although one theory is that this induces PVD [42]. Thus, combining laser coagulation with an intravitreal injection of tPA might increase the likelihood of PVD. The additional effect of the retinal laser photocoagulation would be the breakdown of the blood-ocular barrier with influx of fibrin into the vitreous, which will promote the efficacy of tPA induction of PVD. With this treatment, effective prophylaxis of this challenging disease could be achieved. This hypothetical treatment should be investigated in the future.

D. Retinal Vein Occlusions

As early as 1989, Peyman [43] experimented with tPA in the treatment of experimental branch retinal vein occlusion in rabbit eyes. Garcia-Arumi subsequently used tPA as an adjunct to vitrectomy surgery for retinal vein occlusions in humans [see chapter V.A.6. Vitreous surgery of arterial and venous retino-vascular diseases]. The rationale for intravitreal injection of tPA derives from the fact that due to breakdown of the blood-ocular barrier in eyes with retinal vein occlusion, a large amount of plasmin is generated after injection of tPA. This could induce PVD that might be therapeutic with respect to the macular edema. Indeed, resolution of macular edema following tPA injection has been reported in patients with retinal vein occlusions [36, 44, 45] and is believed to be due to the induction of PVD. This supports the theory that the posterior vitreous cortex plays a role in the pathogenesis of macular edema following retinal vein occlusion [see chapter III.K. Vitreous in retino-vascular diseases and diabetic macular edema]. A similar mechanism has been implicated in diabetic macular edema where the condition improved after tPA-induced PVD [46].

E. Age-Related Macular Degeneration (AMD)

In recent years, wet AMD is treated worldwide by intravitreal anti-VEGF injections to stop leakage and further proliferation of vessels into submacular membranes. Vitreoretinal surgeons treating AMD by extracting subretinal membranes or performing macular translocations [see chapter V.A.1. AMD surgery] reported strong adhesion of the posterior vitreous cortex to the retina from the macula to the midperiphery [47]. Perichon et al. [48], Krebs et al. [49], and Lee et al. [50] confirmed these findings and determined that complete PVD was much more common in dry AMD, while persistent vitreo-macular adhesion was more common in wet AMD. These observations suggest that the posterior vitreous cortex has a pathogenic effect in AMD [see chapter III.G. Vitreous in AMD]. Hypothetically one may suppose that a permanent traction of the tight adhesive vitreous cortex in the macular area may lead to a slow destruction of the subjacent pigment epithelium. This mechanical stress to the underlying retinal pigment epithelium may release higher levels of VEGF, inducing angiogenesis from the choroid into the submacular space with membrane formation [51]. A chronic vitreo-macular traction may also lead to a continuous exposure of free radicals and cytokines or both, inducing a low-grade inflammation as cause for an AMD [52]. Just recently, Schulze et al. [53] described that a previous (at least 8 years before) vitrectomy with a complete removal of the posterior vitreous cortex for different indications has a protective effect against wet AMD. These considerations should be taken into account, to induce PVD in patients with an AMD in one eye, either via vitrectomy or even better by pharmacologic vitreolysis. tPA or ocriplasmin

could be the agent of choice, depending on various clinical considerations.

F. Miscellaneous Conditions

Only one paper by Diaz-Llopis et al. [54] of unsuccessful treatment with autologous plasmin in four patients with premacular membranes and macular pucker has been published. The lack of efficacy probably relates to the fact that most cases of macular pucker already have a PVD. Indeed, anomalous PVD with vitreoschisis [see chapter III.B. Anomalous PVD and vitreoschisis] is believed to be pathogenic in this condition [see chapter III.F. Vitreous in the pathobiology of macular pucker].

Peyman tested intravenous tPA in experimental suprachoroidal hemorrhage [17] and subsequently tested subconjunctival hemorrhage to treat this condition in humans, with negative results [55]. This group has also tested intravitreal tPA to treat experimental bacterial endophthalmitis [56] and premacular retrocortical hemorrhage in shaken baby and battered child syndrome [57].

There are no reports in the literature about the use of tPA alone or in combination with vitrectomy in the therapy of vitreo-macular traction, macular hole, PVR, or retinopathy of prematurity, although the last mentioned has indeed been treated with plasmin [see chapter VI.D.2. Pharmacologic vitreolysis with plasmin: clinical studies].

Abbreviations

AMD	Age-related macular degeneration
bFGF	Basic fibroblast growth factor
cc	Cubic centimeters
DNA	Deoxyribonucleic acid
EU	European Union
FDA	US Food and Drug Administration
L	Liter
mg	Milligrams
MMP	Matrix metalloproteinase
PVD	Posterior vitreous detachment
SF6	Sulfur hexafluoride gas
tPA	Tissue plasminogen activator
U	Units
VEGF	Vascular endothelial growth factor

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