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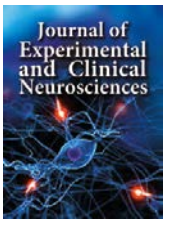

Review Article

A Review on Molecular Mechanisms of Reocclusion Following Thrombolytic Therapy in Ischemic Stroke Patients

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Abstract

Stroke is the second most common cause of death worldwide. Despite many advances in the field of vascular neurology, intravenous (IV) tissue plasminogen activator (tPA) remains the only approved treatment for acute ischemic stroke, even though complications such as hypofibrinolysis and reocclusion, are reported to be as high as 25-34% of cases. The exact mechanisms of unsuccessful thrombolytic therapy are unclear. Some molecular events such as activation of intrinsic and extrinsic pathways C-reactive protein (CRP), thrombin-activatable fibrinolysis inhibitor (TAFI), plasminogen activator inhibitor-1 (PAI-1) are the main causes of failure. Moreover, release of thrombin after tPA therapy, tissue factor pathway inhibitor (TFPI) inhibition, and some gene polymorphisms may play a crucial role in reocclusion. Due to the necessity for development of effective strategies to improve clinical efficacy of tPA therapy, we aimed to evaluate the possible mechanisms, which may be responsible for re-occlusive complications after tPA therapy.

Introduction

Stroke is the second most common cause of death after myocardial infarction and is the leading cause of acquired disability worldwide [1], representing a major economic burden on healthcare systems [2]. In 2010, there were 2.8 million deaths and 39.4 million disability cases reported due to acute ischemic stroke [3]. Without intervention, the number of global deaths is predicted to rise to 6.5 and 7.8 million in 2015 and 2030, respectively [4].The major cause of ischemic stroke is occlusion of cerebral arteries either by a cardiac embolus or by thrombus formation in the atherosclerotic vessel walls [5].

Intravenous (IV) tissue plasminogen activator (tPA) is the only Food and Drug Administration (FDA) approved treatment for acute ischemic stroke [6]. Only about 30% of countries worldwide have reported administration of IV-tPA; this includes 3% of low-income, 19% of lower-middle income, 33% of upper-middle income, and 50% of high-income countries [3].

Published studies have indicated adverse effects and compilations due to the use of tPA [7, 8]. Hypofibrinolysis is one of the important causes for venous and arterial thrombosis [9]. In addition, following the administration of thrombolytic agents, early reocclusion has been observed in the recanalized arteries in some of treated patients [10]. Based on the study by National Institute of Neurological Diseases and Stroke, early (within the first 2 hours) reocclusion rate was 34 % in stroke patients that received IV-tPA, resulting in clinical deterioration and poor long-term outcomes [11].

In addition, endogenous tolerance to tPA may decrease the benefit of thrombolysis-induced recanalization [12]. It seems that some molecular events such as activation of intrinsic and extrinsic pathways [13], tissue factor pathway inhibitor (TFPI) [14], C-Reactive protein [15] and thrombin release after tPA therapy [16] may be involved in this phenomena. Furthermore, thrombin-activatable fibrinolysis inhibitor (TAFI) and plasminogen activator inhibitor-1 (PAI-1) may play a crucial role in the reocclusion process as fibrinolysis inhibitors [12].

According to the recent literature on the subject, genetic polymorphisms in coagulation regulatory enzymes may

influence the outcome in t-PA-induced recanalization in ischemic stroke patients [12].

Due to the need for development of effective strategies to improve clinical efficacy of tPA therapy, the possible underlying pathways and mechanisms responsible for re-occlusion must be further discussed. The aim of this review article is to elucidate the roll of factors involved in reocclusion complications after tPA therapy.

Thrombin and reocclusion

Fibrinolysis is a process that dissolves fibrin, a scaffolding protein involved in clot formation [17]. During fibrinolysis, circulating prothrombin is activated to thrombin which converts soluble circulating fibrinogen into fibrin. Fibrin monomers polymerize to create a meshwork to help stabilize platelet-rich thrombi formed at sites of plaque degradation [16]. Moreover, newly generated thrombin plays an essential role in activating platelets and formation of the new fibrin clots [18]. During the thrombolysis process, thrombin stimulates the release of tissue factor from endothelial cells [19] that activates platelets and facilitates feedback amplification of various stages in clotting cascade [20].

There is a feedback loop between thrombin and factor VIII [21], which may be activated during tPA therapy. Factor VIII contributes further to platelet aggregation and fibrin formation via thrombin generation (see Figure 1) [22]. It seems that some of the autocatalytic procedures may form new clots following recanalization of occluded vessels.

Plasmin and reocclusion

The basic mechanism underlying fibrinolysis by tPA is conversion of plasminogen into plasmin [23]. However at the same time, it has been demonstrated that plasmin may induce activation of factors VII and XII [24]. This activation may provoke the intrinsic and extrinsic pathways, which leads to thrombus formation [25]. Furthermore, plasmin has been shown to activate platelets directly [26].

As factor Xa activates TFPI [27], plasmin could cleave/inactivate TFPI in a time and concentration relevant manner [28, 29]. TFPI inhibits tissue factor-mediated activation of the coagulation pathway, which occurs with plaque rupture. Eventually, TFPI inhibition can increase coagulation in recanalized arteries.

Plasminogen activation can also be inhibited by presence of TAFI [30]. The elevated levels of circulating TAFI in plasma may have an adverse effect on recanalization process after tPA therapy (see Figure 2) [31].

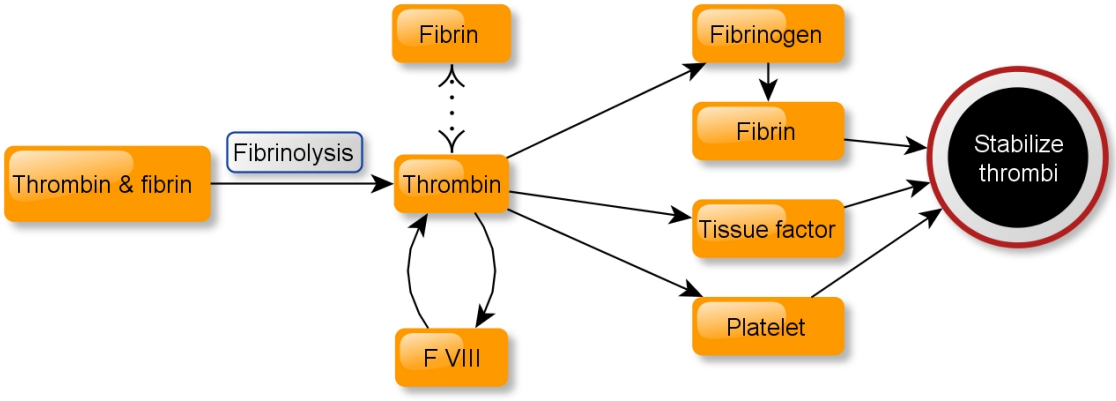

Figure 1. Thrombin related mechanisms for reocclusion that may occur after t-PA therapy; (F VIII) Factor VIII.

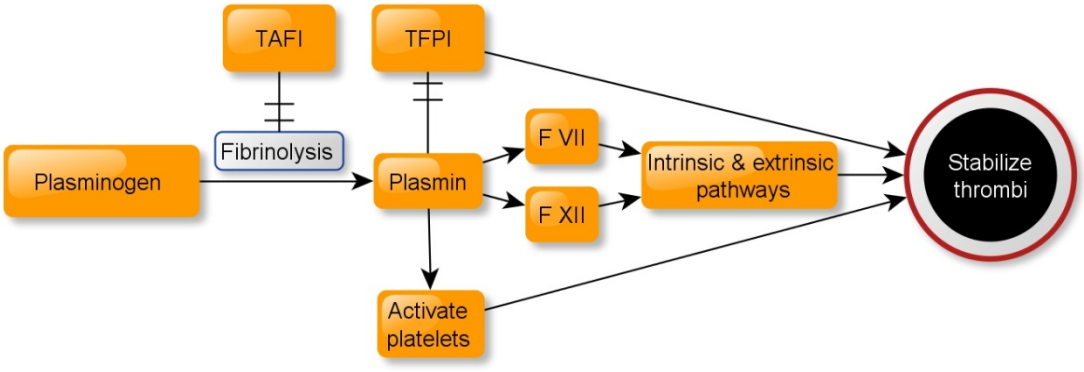

Figure 2. The role of plasmin and fibrinolysis inhibitors in occlusion of recanalized arteries after t-PA administration; (TAFI) Thrombin-activatable fibrinolysis inhibitor; (TFPI) Tissue factor pathway inhibitor; (F VII) Factor VII; (F XII) Factor XII.

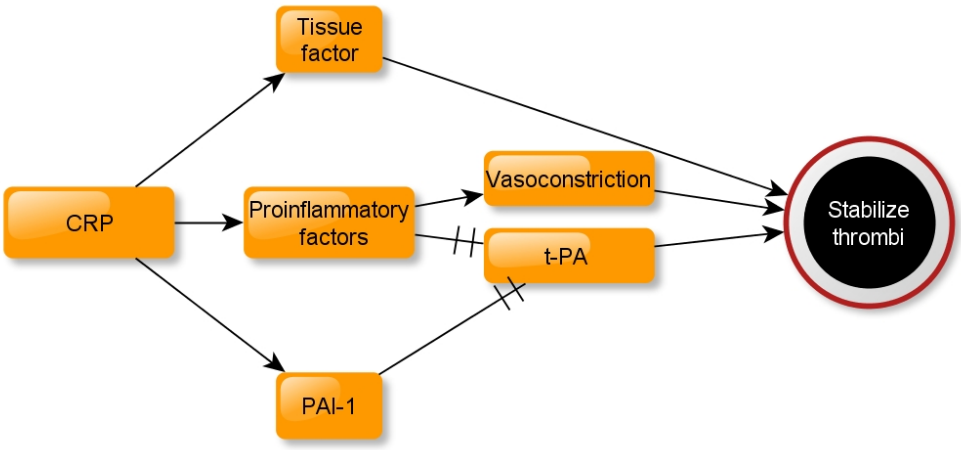

Figure 3. Inflammation role in reocclusion after tPA therapy in ischemic stroke patients. (CRP) C-reactive protein; (PAI-1) Plasminogen activator inhibitor-1.

C-reactive protein and reocclusion

C-reactive protein (CRP) is an acute phase reactant and a blood biomarker for inflammation [32]. High-sensitivity CRP (hs-CRP), has been used as a risk predictor for stroke [33]. This is due to the fact that CRP attenuates fibrinolysis process via direct and indirect pathways. CRP stimulates PAI-1 release from endothelial cells [34]. PAI-1 is a 50-kDa serpin family member protein that inhibits t-PA and u-PA (urokinase-type plaminogen activator) [35]. It should be pointed out that PAI-1 is a key regulator of fibrinolysis by inhibiting t-PA [36]. On the other hand, CRP stimulates tissue factor release from mononuclear cells [34]. Aggregation of tissue factor creates a hypercoagulable state that may lead to reocclusion after t-PA therapy.

Moreover, in stroke patients, during clot formation and after fibrinolysis, pro-inflammatory factors increase in occluded areas [37]. Also, CRP promotes generation of pro-inflammatory cytokines such as IL-1β and TNFα [34] which can strongly inhibit t-PA activity.

Other pro-inflammatory factors such as endothelin increase in cerebroventricular fluid after stroke [38], where increased levels of such mediators may lead to vasoconstriction and reduced tPA therapeutic function (as shown in Figure 3).

Thrombolysis improving strategies

Researchers try to find possible ways to improve the thrombolysis process after ischemic stroke onset. Mechanical dissociation of clot [39] or use of ultrasound methods [40] are proposed in some of the literatures. Continues monitoring with transcranial Doppler (TCD) in combination with tPA therapy show higher recanalization rate than tPA without the use of TCD [41]. Other adjunct modalities such as the use of microspheres/nanobubbles may also increase the chance of recanalization [42].

Recent experimental studies showed that administration of activated protein C (APC) analogs prevent ischemic stroke and extends the therapeutic window of tPA [43]. Some other agents such as neuroserpin and CDP-choline may reduce excitotoxicity, inflammation, as well as blood brain barrier disruption and improve brain plasticity after acute ischemic stroke [44, 45]. All of these supplementary methods may impact re-occlusion rate after thrombolysis, but more studies are necessary to arrive at a concrete recommendation.

Conclusion

Improvement of tPA-therapy effectiveness and reduction of its adverse effects remain a major health care issue. Therefore, development of strategies to overcome this problem has a high priority. Similarly, more preclinical and clinical investigations are necessary to assess possible mechanical and molecular pathways related to reocclusion scenarios. As mentioned, there are clues about the role of various classes of cytokines in the development and formation of clot in normal and pathologic conditions.

Activation of coagulation cascade and infiltration of CRP, TAFI and PAI-1are the determining factors in re-occlusion process after thrombolysis. Moreover, thrombin release after tPA therapy, TFPI inhibition, and some of gene polymorphisms may play role in reocclusion. Although, there is limited information about detailed mechanistic aspects of reocclusion process, attempts were made here to have a brief review on available information.

Conflict of interests: The authors declare no conflict of interest.

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