Plasminogen Activators in Ischemic Stroke

Introduction

Gregory J. del Zoppo, MD

A number of plasminogen activators (PAs), enzymes capable of converting the zymogen plasminogen to the active agent plasmin, have been studied as potential therapeutic agents in the settings of ischemic stroke, intracerebral parenchymal hemorrhage, and large vessel thrombosis. Several have found purpose in the acute management of focal cerebral ischemia under strictly limited conditions. All derive from naturally occurring PAs that can generate plasmin in the circulation or in fibrin clots, and all are known to lyse thrombi. This session examines potential modifications to accepted strategies for the treatment of ischemic stroke acutely.

The principles for the acute use of PAs in ischemic stroke derive from the common understanding of plasminogen activation in the circulation and in thrombi known to target in situ thrombotic occlusions. Physiologically, the intrinsic (endothelial) thrombolytic system entails the secretion of single-chain urokinase (sc u-PA) and of single-chain tissue type plasminogen activator (sc t-PA) from endothelial cells.1-3 These precursor PAs are converted to urokinase (u-PA) and t-PA by locally derived plasmin. Plasmin is itself generated from the inactive zymogen plasminogen by u-PA and/or t-PA (Figure). The formation of plasmin from plasminogen is the central reaction necessary for thrombus lysis. This conversion is highly regulated under ordinary circumstances. For instance, plasminogen activator inhibitor-1 and -2 directly inhibit the actions of u-PA and t-PA to convert plasminogen to plasmin.4,5 When t-PA is bound to fibrin and plasminogen (fibrin-bound plasminogen) in a ternary complex, both t-PA and plasmin are protected from their respective inhibitor systems.6 In the circulation, plasmin is inhibited by α2-antiplasmin, which blocks the binding of plasminogen to the surface of the thrombus.7

Plasmin catalyzes the proteolysis of fibrinogen and fibrin in a specific fashion.8 Circulating fibrinogen is converted by plasmin to fragment X (which consists of fragments Y and D), in addition to the Bβ1 to 42 and Aα fragments. Fragment Y is further converted to fragments D and E as end-products of fibrinogenolysis. These degradation products reflect the degradation of fibrinogen specifically. Degradation of the fibrin framework in thrombi generates the DED (p-dimer) fragments from cross-linked fibrin, when the thrombus is formed.9 Additionally, plasmin has been shown to degrade coagulation factors I (fibrinogen), V, and VIII, and von Willebrand factor.

Plasmin can play several roles in matrix biology also. This protease has been reported to degrade myelin basic protein, and the extracellular matrix proteins laminins, type IV collagen, perlecan, vitronectin, and fibronectin.10-16 In addition, plasmin can activate the inactive gelatinase pro-matrix metalloprotease (pro-MMP)-9 to MMP-9, and can activate MT1-MMP (which itself activates pro-MMP-2). Hence, plasmin generated locally could facilitate gelatinase-dependent degradation of the vascular matrix proteins collagen IV, laminins, and fibronectin. Sappino et al demonstrated a region-specific localization of plasminogen in the murine central nervous system,17 suggesting that tissue sources could play roles in cell-cell interactions (eg, signaling) and in responses to injury. Interestingly, while the microvessel endothelial expression of t-PA is relatively low,18 during focal cerebral ischemia tissue t-PA content does not increase from low baseline levels, whereas both u-PA and plasminogen activator inhibitor-1 content do.19 The extent to which hyperplasminemic states can alter cerebral vascular integrity is yet to be rigorously studied. Nonetheless, the actions of plasminogen activators to generate plasmin can affect both in situ thrombus as well as vascular matrix biology.

In addition to endogenous thrombolytic substances, a group of now well-known exogenous plasminogen activators, which derive from these PAs, have found roles in safety and efficacy trials in ischemic stroke (Table 1). Among the recognized PAs, to date only rt-PA is approved for use in the acute treatment of ischemic stroke.

Considerations for the use of PAs in the setting of ischemic stroke paralleled successful studies of their utility in the acute treatment of myocardial ischemia. Reconsideration of the potential utility of u-PA and streptokinase took place in the late 1970s and early 1980s following reports that urokinase was unsafe in the setting of cerebral ischemia.20 Applying the concept that acute intervention (within 6 hours of stroke symptom onset) could ameliorate the injury caused by thrombotic or thromboembolic occlusion,21 groups in North America, Germany, and Japan working separately and together demonstrated the feasibility and relative safety of...
either directed intra-arterial or intravenous acute PA infusion in thrombotic and thromboembolic stroke.22,23 Mori et al first indicated the ability of recombinant 2-chain t-PA (duteplase) to achieve recanalization with clinical benefit, and no excess safety concerns, compared to placebo in a prospective randomized blinded clinical trial.24 In parallel, a dose-rate improvement in the lysis of distal carotid territory occlusions, without an increase in hemorrhagic transformation, was demonstrated with intravenous infusion of rt-PA (duteplase).25

During this early development of the potential of PAs in focal ischemia in the central nervous system, a number of concepts and problems were considered that are relevant to current practice (Table 2): (1) the safety of the PA under test and strategies for enhancing the safety of specific PAs in the central nervous system, (2) the relative importance of thrombus-selectivity in acute thrombus lysis, (3) strategies for optimizing PA delivery for the best and safest thrombus lytic effect, (4) whether specific thrombus lytic effects of different PAs could alter outcome, (5) the potential extravascular effects of rt-PA in the central nervous system, and (6) considerations for appropriate patient selection. While the last 3 decades have seen significant work on several of these problems (particularly agent delivery and altered thrombus lytic effect of specific PAs), these issues are still highly relevant for current and future practice.

In this session, the 5 presentations address further design concerns that were also central to the early development of a role for PAs in the acute treatment of ischemic stroke. Dr Marder will present data concerning the role(s) that plasmin could play in thrombus lysis, from animal model work in his group. Drs Lanza and Holland, respectively, will discuss delivery of PAs with nanoparticles and enhancing thrombus-lytic effect with ultrasound. The possible role of annexin II(A2) in the thrombus lytic effect of PAs will be discussed by Dr Wang. Finally, the clinical use of rt-PA in stroke patients, as related to patient selection, will be considered by Dr Johnston. Each of these presentations offers evidence for possible refinements in how the PA-mediated positive outcomes in ischemic stroke might be safely enhanced.

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Disclosures

None.

References


Table 1. Fibrin(ogen)olytic Agents Tested in Ischemic Stroke

<table>
<thead>
<tr>
<th>Exogenous Plasminogen Activators</th>
<th>u-PA</th>
<th>SK</th>
<th>rt-PA</th>
<th>r-PA</th>
<th>TNK</th>
<th>rDS-PA</th>
<th>STK</th>
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<tbody>
<tr>
<td>Urokinase</td>
<td></td>
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<td>Tissue plasminogen activator*</td>
<td>Reteplase</td>
<td>Tenecteplase</td>
<td>Desmodus sp PA* (desmoteplase)</td>
<td>Staphylokinase</td>
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<td>SCU-PA</td>
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<td>Single chain urokinase (pro-urokinase)*</td>
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<td>STK</td>
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*Recombinant.

Table 2. Issues in Testing Thrombus Lytic Agents

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<tr>
<th>Plasminogen Activation in CNS Concerns in Design</th>
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<td>Enhancing the safety of the plasminogen activator</td>
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<td>Thrombus-specificity and thrombus lysis in cerebral arteries</td>
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<td>Optimizing delivery for thrombus-lytic effect</td>
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<td>Thrombus lytic effect of plasminogen activator</td>
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<td>Extravascular effects of rt-PA in the CNS</td>
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<td>Patient selection</td>
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Figure. Mechanisms of endogenous plasminogen activation. Single-chain urokinase (sc u-PA) and single-chain tissue type plasminogen activator (sc t-PA) derive from endothelial cells. The primary process is the activation of the zymogen plasminogen to plasmin, which in turn cleaves fibrinogen and fibrin to specific fibrin(ogen) degradation products (FDP). Plasmin interacts with other substrates that it can activate or degrade variously. These include the matrix proteins collagen type IV, laminin (LN), perlecan, and fibronectin (FN).

Key Words: acute Rx, acute stroke, brain, cerebral infarct, embolic stroke, stroke management, tPA
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