α2 Antiplasmin and Microvascular Thrombosis in Ischemic Stroke

Enming J. Su, Daniel A. Lawrence

Stroke occurs in 2 forms, ischemic and hemorrhagic, with ≈87%, being of ischemic origin.1 Ischemic strokes are characterized by the rapid onset of focal neurological symptoms, and the prompt restoration of blood flow should be the most effective approach for treating ischemic stroke. Currently, tissue-type plasminogen activator (tPA), a highly specific serine protease of the fibrinolytic cascade, is the only thrombolytic agent approved by the US Food and Drug Administration for the treatment of ischemic stroke.2 However, emerging evidence has suggested that the beneficial effects of reperfusion associated with thrombolytic treatment are counterbalanced by potentially harmful activities of tPA,3–7 including a significant increase in the risk of hemorrhagic conversion, a serious complication that is associated with high mortality.8,9 Thus, although treatments, such as thrombolysis and thrombectomy, have been successful, it is estimated that <5% of ischemic stroke patients receive treatment,3 and 1 major reason for this low percentage is the risk of hemorrhagic conversion.

See accompanying article on page 2586

The mechanism by which tPA works to restore vascular patency and reperfusion is straightforward and well understood.10 tPA activates plasminogen to plasmin, which in turn dissolves the occluding thrombus to recanalize the blocked vessel (Figure). Factors that modulate plasmin activity would therefore be expected to act in the same pathway as tPA and to contribute to the fate of clot dissolution and stroke outcome in a manner consistent with modulation of tPA activity. However, an earlier study in mice genetically deficient in either tPA or the plasmin inhibitor, α2-antiplasmin (α2AP), had paradoxically suggested that removing profibrinolytic, tPA, or antifibrinolytic, α2AP, would therefore be expected to act in the same pathway as tPA and to contribute to the fate of clot dissolution and stroke outcome in a manner consistent with modulation of tPA activity. However, an earlier study in mice genetically deficient in either tPA or the plasmin inhibitor, α2-antiplasmin (α2AP), had paradoxically suggested that removing profibrinolytic, tPA, or antifibrinolytic, α2AP, has similar beneficial outcomes in a murine model of stroke.11 The report by Reed et al12 in this issue addresses the role of α2AP in a model of embolic stroke and provides important new mechanistic insight into how α2AP affects stroke outcome.

Previous studies of α2AP in stroke have been relatively limited and focused primarily on following hemostatic factors during stroke. One exception is the work of Nagai et al13,14 who have studied the effects of reducing α2AP in animal models of stroke with antibodies or with microplasmin, and a phase 1 clinical trial has been reported testing the safety of the latter approach.14 Nonetheless, the idea of targeting α2AP has not received much attention. This may be because α2AP supplementation was shown to reduce bleeding complications in a rabbit model of thrombosis with tPA,15 or possibly because it is counterintuitive that reducing a systemic plasmin inhibitor would be a safe alternative to thrombolysis.16 What Reed et al12 add to the story is the importance of secondary microvascular thrombosis to infarct size and how α2AP affects this process. Their data suggest that secondary microvascular thrombosis in the ischemic penumbra plays a critical role in infarct expansion, and that enhancing endogenous fibrinolysis by reducing α2AP activity can significantly improve stroke outcome. To achieve this, plasma α2AP activities were modulated either genetically with α2AP−/− mice, or via intravenous infusion of recombinant α2AP, creating different circulating levels of α2AP in mice.

In addition, the authors elegantly differentiate the effects of circulating and thrombus-bound α2AP on stroke.12 To accomplish this, the authors generate artificial thromboemboli made from normal plasma or α2AP-deficient plasma and then inject these into the middle cerebral artery of α2AP−/− mice. Their data indicate that thrombus-bound α2AP is less important than circulating α2AP for infarct size, even if clot bound α2AP is critical for dissolution of the primary thrombus. This result further illustrates the importance of secondary microthrombi formed downstream of primary thrombus for stroke evolution.

Despite this interesting and important concept, several limitations of the study should be taken into account. For instance, this study does not differentiate between possible effects of α2AP in the vascular compartment or in brain parenchyma. In addition, this thromboemboli stroke model is an extreme example of ischemic stroke with high mortality rates. For example, in tPA-treated mice mortality reached 100% by 50 hours after treatment, whereas control mice, mortality reached >65%, both of which are much higher than in other experimental models or in the clinic.

Still, the study by Reed et al provides the reader with the interesting and important concept that inhibiting circulating α2AP may promote endogenous fibrinolysis in downstream areas of secondary thrombosis and that this may reduce infarct expansion. Finally, it is interesting to note that hemorrhage in this model was significantly worse in mice receiving tPA than in mice completely deficient in α2AP. This suggests that the simple concept that tPA induces hemorrhage by promoting unregulated plasmin activity may not be correct and supports the hypothesis that the association of thrombolytic tPA with an increased risk of hemorrhage may be because of tPA’s action on substrates other than plasminogen.17 Whether inhibiting α2AP may be useful for treating ischemic stroke in the

From the Department of Internal Medicine, Division of Cardiovascular Medicine, University of Michigan Medical School, Ann Arbor.

Correspondence to Daniel A. Lawrence, PhD, Department of Internal Medicine, Division of Cardiovascular Medicine, University of Michigan Medical School, 7301 MSRIB III, 1150 W Medical Center Dr, Ann Arbor, MI 48109-5644. E-mail dlawrenc@umich.edu


© 2014 American Heart Association, Inc.

Arterioscler Thromb Vasc Biol is available at http://atvb.ahajournals.org
DOI: 10.1161/ATVBAHA.114.304616

Enming J. Su, Daniel A. Lawrence


Enming J. Su, Daniel A. Lawrence


Enming J. Su, Daniel A. Lawrence


Enming J. Su, Daniel A. Lawrence


Enming J. Su, Daniel A. Lawrence


Enming J. Su, Daniel A. Lawrence


Enming J. Su, Daniel A. Lawrence


Enming J. Su, Daniel A. Lawrence


Enming J. Su, Daniel A. Lawrence

clinic remains to be seen; however, to the extent that stroke evolution is dependent on microvascular thrombi formation, than agents promoting endogenous fibrinolysis are certainly worth further study.

Disclosures

None.

References


Key Words: alpha-2-antiplasmin ■ cerebrovascular disorders ■ stroke ■ thrombosis
α2 Antiplasmin and Microvascular Thrombosis in Ischemic Stroke
Enming J. Su and Daniel A. Lawrence

Arterioscler Thromb Vasc Biol. 2014;34:2522-2523
doi: 10.1161/ATVBAHA.114.304616
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/34/12/2522

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at:
http://atvb.ahajournals.org/subscriptions/