Blood Pressure Reduction and Tissue-Type Plasminogen Activator Release

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Hypertension is associated with increased risk of thrombotic events including myocardial infarction and stroke. The endothelium plays an important role in limiting intravascular thrombosis, inhibiting coagulation and platelet aggregation, and promoting fibrinolysis. Hrafnkelsdottir et al have previously described impaired vascular tissue-type plasminogen activator (t-PA) release in individuals with essential hypertension. In the current issue of Hypertension, this group reports that treatment with either an angiotensin-converting enzyme (ACE) inhibitor or a calcium channel blocker increases stimulated t-PA release from the forearm vasculature.

t-PA is synthesized and stored in small, dense granules in the vascular endothelium and released in response to such stimuli as Factor Xa, thrombin, bradykinin, and catecholamines, as well as substance P, the vasopressin analogue desmopressin, methacholine, tumor necrosis factor α, and adenosine and uridine triphosphates (Figure). Although some studies suggest that t-PA colocalizes with von Willebrand factor in Weibel-Palade bodies, the preponderance of evidence suggests that t-PA is stored in distinct granules and that the release of t-PA and von Willebrand factor are differentially regulated. Although shear stress induces t-PA release from cultured endothelial cells, t-PA release from the intact vasculature appears to be flow independent. NO does not stimulate t-PA release and may even impede the exocytosis of t-PA. t-PA is rapidly released in response to increases in intracellular calcium, but the molecular mechanisms underlying the exocytosis of t-PA have not been elucidated in detail.

The measurement of agonist-stimulated vascular t-PA release in the forearm has provided a useful research tool with which to assess the effects of disease and interventions on vascular endothelial fibrinolytic capacity. Importantly, t-PA release from the forearm vasculature reflects t-PA release from the coronary vasculature. Stimulated vascular t-PA release is diminished not only in hypertension but also in smoking and obesity, and deficits in stimulated t-PA release may precede impairment of endothelial-dependent vasodilation. Conversely, Ridderstråle et al observed that antihypertensive therapy improved endothelial fibrinolytic function without affecting vasomotor function. In contrast to endothelial-dependent vasodilation, t-PA release is not impaired in hypercholesterolemia. Stimulated t-PA release is similar in black and white ethnic groups and may be increased in women compared with men. Whether stimulated t-PA release predicts future cardiovascular events remains to be determined.

The data of Ridderstråle et al highlight the inadequacy of peripheral measurements of t-PA antigen concentration or activity to assess endothelial fibrinolytic capacity. In their study, antihypertensive therapy did not affect circulating t-PA antigen or activity, although substance P-stimulated t-PA release was doubled. After release, active t-PA complexes rapidly with its inhibitors, predominantly plasminogen activator inhibitor (PAI) 1, and free t-PA is cleared more rapidly than the t-PA:PAI-1 complex, such that peripheral t-PA antigen and activity measurements reflect prevailing PAI-1 concentrations. Measurement of agonist-stimulated t-PA release in the forearm provides a precise measure of endothelial fibrinolytic function; however, the invasiveness of brachial arterial cannulation and infusion precludes widespread application of the method.

Prior studies indicate that either acute or chronic ACE inhibition enhances bradykinin-stimulated t-PA release, presumably by decreasing the degradation of bradykinin but also by increasing receptor sensitivity. In addition, acute ACE inhibition increases basal t-PA release in women via endogenous bradykinin. The finding of Ridderstråle et al extends this literature in several ways. The study is the first to report the effect of ACE inhibition or calcium channel blockade on endothelial fibrinolytic function in essential hypertension. The authors used substance P rather than bradykinin as the agonist to assess stimulated t-PA release. Because ACE cleaves substance P, it is not possible to exclude potentiation of substance P–stimulated t-PA release via a pharmacokinetic mechanism in those subjects treated with the ACE inhibitor; however, ACE inhibition does not potentiate substance P–stimulated t-PA release in congestive heart failure patients, and, thus, it is likely that the effects they observed reflect a pharmacodynamic action of blood pressure lowering rather than a pharmacokinetic action of ACE inhibition.

Moreover, Ridderstråle et al found that antihypertensive treatment with either an ACE inhibitor or a calcium channel blocker augmented stimulated t-PA release, suggesting that blood pressure reduction alone enhances endothelial fibrinolytic function and that improvement in endothelial fibrinolytic function is not drug class–dependent. On the one hand, this finding is consistent with ex vivo data indicating that increased intraluminal pressure decreases t-PA expression and release in human umbilical veins or cultured endothelial cells. On the other hand, the small size and heterogeneity of the study groups does not permit a direct comparison of the
effects of the 2 agents, and the time-to-peak t-PA release was significantly diminished only during ACE inhibition.

Improvement of endothelial fibrinolytic capacity represents 1 mechanism whereby antihypertensive therapy can decrease the incidence of thrombotic events. Larger clinical studies are needed to address definitively the question of antihypertensive versus class effect. At a fundamental level, understanding the molecular mechanisms underlying stimulated t-PA release could lead to additional pharmacological strategies to improve endothelial fibrinolytic function. Furthermore, the development and prognostic validation of accurate but non-invasive, methodologies to assess endothelial fibrinolytic function would provide an accessible “biomarker” for risk of thrombotic events in clinical trials of antihypertensive agents.

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References
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