Mechanism of Cadmium Stimulation on the Production of Fibrinolytic Proteins in Vascular Endothelial Cells

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Introduction

Damage of vascular endothelial cell layers induces blood coagulation but the fibrin clot is degraded by plasmin. This fibrinolytic activity is regulated at the step of conversion of plasminogen to plasmin by tissue plasminogen activator (t-PA). Cadmium and lead have been reported to induce vascular lesions such as atherosclerosis. Since vascular lesions and a procoagulant state of blood have a strong interrelationship, we studied the toxicity of cadmium and lead on the fibrinolytic system regulated by vascular composing cells.^{1–4)} In the present study, we investigated the mechanism of cadmium stimulation on the production of fibrinolytic proteins by vascular endothelial cells in culture.

Methods

Confluent cultures of human umbilical vein endothelial cells were treated with cadmium chloride for 24 h in a serum-free medium. After treatment, antigens of t-PA and plasminogen activator inhibitor-1 (PAI-1) accumulated in the medium were measured by enzyme immunoassay. Activity of t-PA in the medium was determined by fibrin zymography. Expression of t-PA and PAI-1 genes was analyzed by reverse transcription-polymerase chain reactions.

Results and Discussion

Cadmium significantly increased the PAI-1 release without changing the t-PA release, and as a result, t-PA activity in the medium was decreased by the metal. Basic fibroblast growth factor suppressed the release of both t-PA and PAI-1⁵⁾ while endothelin suppressed only the t-PA

release.⁶⁾ In addition, cadmium stimulation of the PAI-1 release occurred even in the presence of anti-transforming growth factor- β antigen, suggesting that involvement of these autocrine factors in cadmium stimulation can be ignored. Cadmium accumulated within vascular endothelial cells in a dose-dependent manner. At that time, expression of t-PA gene was unchanged but that of PAI-1 gene was markedly enhanced. Cadmium stimulation of the PAI-1 release disappeared in the presence of actinomycin D, an inhibitor of mRNA synthesis. Induction of PAI-1 gene expression and the PAI-1 release by cadmium were completely suppressed by H-7, a strong protein kinase C inhibitor, but not by HA1004, a weak inhibitor. The present data suggested that intracellular cadmium directly activates the protein kinase C pathway and selectively stimulates the production of PAI-1 at the transcriptional level in vascular endothelial cells.

References

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