Stimulatory Effect of Cadmium on the Release of Plasminogen Activator Inhibitor-1 from Cultured Human Vascular Endothelial Cells

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Introduction

Fibrinolysis depends on the balance between tissue plasminogen activator (t-PA) and plasminogen activator inhibitor-1 (PAI-1) released from vascular endothelial cells. When the balance is lost, the vascular endothelium may be damaged through a thrombogenic state. Although cadmium is known to induce vascular lesions in vivo, it has not been clear whether or not cadmium can cause functional damage in endothelial cells. We reported that cadmium destroys the monolayer of cultured endothelial cells. The present study investigated the effect of cadmium, at the level where the cytotoxicity was not observed, on the release of t-PA antigen (t-PA:Ag) and PAI-1 antigen (PAI-1:Ag) from cultured endothelial cells.

Methods

Vascular endothelial cells from human umbilical vein were cultured until confluent and incubated for 24 h in Dulbecco's modified Eagle's medium supplemented with 1% BSA in the presence or absence of cadmium chloride (0.5, 0.1 or 2.0 μM). After incubation, the content of t-PA:Ag and PAI-1:Ag released from the cells into the medium was determined by EIA. The PA activity was assayed using D-But-CHT-Lys-pNA as substrate.

Results

Cadmium at 1.0 and 2.0 μM significantly increased the release of PAI-1:Ag but not t-PA:Ag from cultured endothelial cells after a 24-h incubation. Cadmium (1.0 μM)-induced increase in the PAI-1:Ag release was observed after 24 h but did not occur after 6 h and less. Of tested heavy metals including cadmium, nickel, cobalt, copper and zinc at 1.0 μM each, cadmium and nickel significantly increased the PAI-1:Ag release, with the effect of cadmium being stronger than that of nickel. The other metals failed to affect the PAI-1:Ag release. Incorporation of [3H]-leucine into the acid-insoluble fraction of the cell layer was not changed by cadmium. Cadmium at both 1.0 and 2.0 μM reduced the PA activity in the medium after a 24-h incubation.

Discussion

Cadmium was found to increases the PAI-1:Ag release from cultured vascular endothelial cells, while the t-PA:Ag release was not changed. The stimulation of the PAI-1:Ag release was observed in cadmium and nickel but not in other heavy metals. It was therefore suggested that the release of t-PA:Ag and PAI-1:Ag is not necessarily coupled, and that each heavy metal acts on endothelial cells in an independent manner. The incorporation of [3H]leucine and the activity of LDH in the medium were not changed by cadmium, suggesting that the metal-induced increase in the endothelial PAI-1:Ag release was not due to either the nonspecific stimulation of protein synthesis or a response to the cytotoxicity. Cadmium-induced reduction of the PA activity in the medium suggests that the metal may induce a procoagulant or fibrinolytic state on the surface of vascular endothelium. In conclusion, it was shown that cadmium stimulates the endothelial release of PAI-1:Ag but not that of t-PA:Ag. The mechanism of cadmium stimulation of PAI-1:Ag release was not clear, however, these findings will help the interpretation of cadmium-induced vascular lesion which may be mediated by an anti-fibrinolytic state.

References