

Abstract

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Endogenous nitric oxide synthesis inhibitor asymmetric dimethyl L-arginine accelerates endothelial cell senescence.

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OBJECTIVE: Asymmetrical dimethylarginine (ADMA) is an endogenous inhibitor of nitric oxide synthase (NOS), and its accumulation has been associated with cardiovascular disease. We aimed to investigate the role of ADMA in endothelial cell senescence.

METHODS AND RESULTS: Endothelial cells were cultured until the tenth passage. ADMA was replaced every 48 hours starting at the fourth passage. ADMA significantly accelerated senescence associated beta-galactosidase activity. Additionally, the shortening of telomere length was significantly accelerated and the telomerase activity was significantly reduced. This effect was associated with an increase of oxidative stress: allantoin, a marker of oxygen free radical generation, and intracellular reactive oxygen species (ROS) increased significantly after ADMA treatment compared with control, whereas cellular thiol status and NOx synthesis decreased. Furthermore, ADMA-increased oxidative stress was accompanied by a decrease in the activity of dimethylarginine dimethylaminohydrolase (DDAH), the enzyme that degrades ADMA, which could be prevented by the antioxidant pyrrolidine dithiocarbamate. Exogenous ADMA also stimulated secretion of MCP-1 and interleukin-8. Coincubation with the methyltransferase inhibitor S-adenosylhomocysteine abolished the effects of ADMA.

CONCLUSIONS: These data suggest that ADMA accelerates senescence, probably via increased oxygen radical formation by inhibiting nitric oxide elaboration. This study provides evidence that modest changes of intracellular ADMA levels are associated with significant effects on slowing endothelial senescence.

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