Hyperhomocysteinemia Enhanced Alveolar Cell Apoptosis via Endoplasmic Reticulum Stress and Exaggerated Cigarette Smoke-Induced Pulmonary Emphysema

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Background and objectives. Previous studies investigated that homocysteine (Hcy) is associated with the pathogenesis of COPD. But its mechanism has not been clarified. Although Hcy is reported to cause endoplasmic reticulum stress (ER stress) and apoptosis to cells such as endothelial cell and hepatocyte, little has been reported on effect of Hcy on alveolar cells and its interaction with cigarette smoking. The aim of study is to investigate the effect of homocysteine and smoking exposure on alveolar cells. Methods. We planed In vivo study and In vitro study. Seven- to nine-week-old C57BL6 male mice were induced hyperhomocysteinemia by giving 1% L-methionine (Met) and were exposed to air or cigarette smoke (CS) for 6 months. Then measurement of blood homocysteine concentration and histological evaluation of emphysematous changes in the lungs were performed. A549 cells (Human alveolar epithelial cell line) were cultured with homocysteine and exposed with cigarette smoking extract (CSE). Subsequently, cell viability and expression of proteins related to the ER stress was evaluated. Results. Plasma levels of Hcy were significantly elevated in the mice that given 1% Met water. And mean linear intercept, as a measure of the interalveolar septal wall distance, was significantly increased in the group exposed to cigarette smoke under the condition of hyperhomocysteinemia compared to the group with cigarette smoke exposure alone. The percentage of apoptotic A549 cells increased as the concentration of Hcy increased and that was augmented by CSE. The expression of ER stress associated protein such as GRP78 and CHOP were increased in A549 cultured with homocysteine and exposed with CSE. The expressions of these proteins were reduced by co-treatment with Vitamin B12 and folate.Conclusion. HHcy may cause pulmonary emphysema and decrease in lung function induced by smoking exposure because of increasing apoptosis of alveolar cells due to the addition of endoplasmic reticulum stress.

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