

Streszczenie w języku angielskim

Extranuclear histones may play a role in the progression of various diseases, including neurodegenerative disorders, where histone H1 is released into the extracellular space, affecting neurons and microglia. Elevated homocysteine (Hcy) have been linked to more than 100 disorders. Hyperhomocysteinemia (HHcy, Hcy>15 μ M) is a risk factor for cardiovascular and neurodegenerative diseases. The objective of this study was to evaluate the potential influence of HHcy on extracellular histones, which could have implications for disease progression. The study was conducted on HUVEC and N2A AD cell lines grown in hyperhomocysteinemic conditions, plasma, brain, liver and spleen from the Apoem1Un (ApoE KO) and SOD1G93A (SOD1) mouse models and human plasma from patients with venous thromboembolism (VTE). Hcy was quantified by HPLC, while levels of extranuclear histones were analyzed by Western blotting and immunohistochemistry. The cell viability and size were assayed with Countess 3 instrument, while histone PTMs were examined via LC-MS/MS. Treatment of cells with Hcy and HTL increased histone H1 expression and its nuclear transport. Stress induced by Hcy resulted in increased H1 levels in the cytoplasm and medium, whereas HTL increased H1 levels only in the cytoplasm. Cells cultured with histone and N-Hcy-histone showed increased tHcy levels in the medium. In vivo models showed a significant increase in extranuclear H1, anti-H1 IgG and tHcy in plasma. ApoE KO mice showed increased tHcy levels in the liver and spleen, while SOD1 mice showed increased tHcy in the liver and decreased levels in the spleen compared to controls. Both in vivo models showed significant increases in extranuclear H1 and H3 levels in all tissues analyzed, except for H3 levels in the liver of ApoE KO mice, which showed no significant change. Elevated Hcy and HTL levels affected histone PTMs, leading to protein dysfunction. Higher levels of histone H1 and anti-H1 IgG were observed in the plasma of VTE patients with HHcy compared to those with normal Hcy levels. Homocysteine and age were determinants of elevated plasma H1 levels in individuals with VTE. The results indicate a significant association between homocysteine and extranuclear histones, suggesting their potential use as biomarkers of disease progression.

Key words: extranuclear histones, homocysteine, neurodegenerative diseases, cardiovascular diseases