외국 연수회원 연구발표

동맥경화 동물모델에서 Humanin의 대동맥 내피기능 보호효과

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Humanin Improve Aortic Endothelial Function in Hypercholesterolemic Apolipoprotein E-deficient Mice

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Humanin (HN) is a 24 amino acid peptide originally isolated from a cDNA library of surviving neurons of familial Alzheimer's disease and is expressed from an open reading frame within the mitochondrial 16S ribosomal RNA. HN is expressed in the endothelial cell layer of human vessels but its role in atherogenesis in vivo is unknown. HN reduced oxidized-LDL induced formation of reactive oxygen species and apoptosis in vitro. The present study tested the hypothesis that long term treatment with HN will have a protective role against endothelial dysfunction and progression of atherosclerosis in vivo.

After daily intraperitonial injection of the HN analogue HNGF6A for 16 weeks, endothelium-dependent relaxation of proximal aorta to acetylcholine was impaired in ApoE-deficient, high cholesterol diet, and saline treated mice (ApoE HC S) compared with control group (Control). HN supplementation in ApoE-deficient, high cholesterol diet, and HN treated mice (ApoE HC HN) significantly enhanced response to acetylcholine compared with ApoE HC S without showing direct vasoactive effects or cholesterol-reducing effects (Fig. 1). HN decreased atherosclerotic plaque size in proximal aorta of ApoE HC HN (Fig. 2).

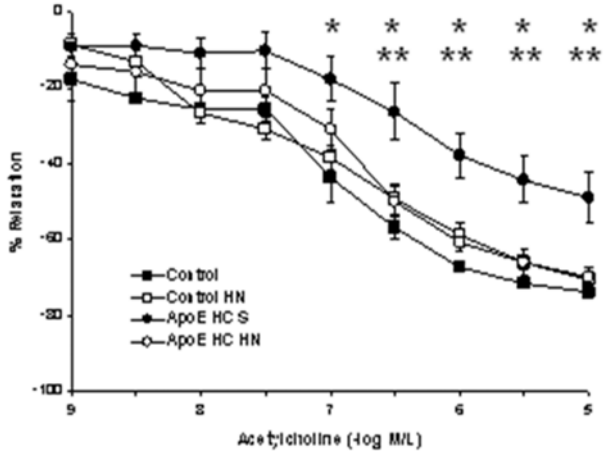

Fig. 1. Endothelium-dependent relaxation of proximal aorta to acetylcholine.

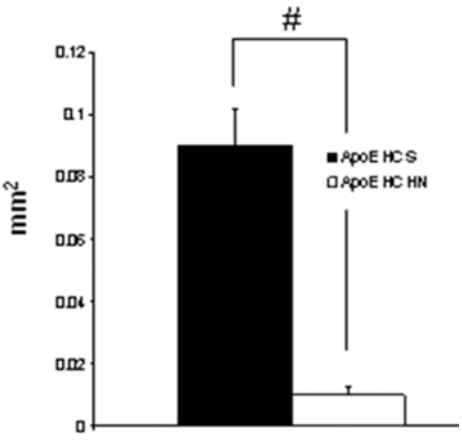

Fig. 2. Atherosclerotic plaque size in proximal aorta.

In immunohistochemistry, HN was expressed in the endothelial cell layer on the aortic plaques. HN treatment reduced apoptosis and nitrotyrosine immunoreactivity in the aortic plaques without affecting the systemic cytokine profile. To confirm the role of HN in cardiovascular health in humans, we measures circulating HN levels and showed that they were 50% lower in patients with coronary endothelial dysfunction compared with subjects with normal coronary endothelial function.

In conclusion, HN may have a protective effect on endothelial function and progression of atherosclerosis by modulating oxidative stress, apoptosis and inflammation in the developing plaque.