［課程－２］

審査の結果の要旨

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This study aimed to evaluate vagus nerve stimulation (VNS) as a therapeutic approach for atherosclerosis prevention. For the *in vivo* experiments, long-term VNS was applied to an atherogenic mouse model (ApoE-KO). GTS-21, a specific agonist of α7 nicotinic acetylcholine receptor (α7nAChR) was used to stimulate monocytes and endothelial cells to mimic VNS *in vitro*. The results are shown below:

1. Long-term VNS reduced body weight and lowered plasma lipid content, including triglycerides and high-density lipoproteins, in ApoE-KO mice. Unexpectedly, long-term VNS increased atherosclerotic plaque formation in the aorta by an unknown mechanism.
2. GTS-21 treatment inhibited the mRNA expression level of integrins (*SELPLG, ITGAM, ITGA4*) in U-937 cells and its adhesion to endothelial cells. The detailed mechanism may be by the inhibition of *RUNX3*, a positive transcriptional regulator of *ITGA4* and *ITGAL*.
3. GTS-21 treatment inhibited the mRNA expression level of adhesion molecules (*ICAM-1*, *VCAM-1*) in HUVECs and reduced monocyte adhesion on HUVECs. Using RNA-seq analysis, it was found that a long non-coding RNA called *SNGH9* might be involved in this mechanism. Knockdown of *SNGH9* in HUVECs showed profound effects in preventing endothelial dysfunction caused by TNFα treatment, and reduced their adhesion ability and expression level of adhesion molecules.

In conclusion, this study proves that stimulation of α7nAChR in monocytes or endothelial cells reduces their adhesion to each other, and molecules *RUNX3* and *SNHG9* were found to mediate this adhesion inhibition in monocytes and endothelial cells, respectively. Additionally, *SNHG9* might be a promising therapeutic target for endothelial dysfunction in vascular diseases. The results of the *in vivo* experiments, for the first time, suggest that using VNS in patients with complications such as obesity or hyperlipidemia may result in similar adverse effects. This research provides a comprehensive evaluation of the application of VNS to the prevention of atherosclerosis both *in vivo* and *in vitro* and reveals certain underlying mechanisms, which have not been described by others.

よって本論文は博士（ 医学 ）の学位請求論文として合格と認められる。