博士論文（要約）

The role of vagus nerve stimulation through acetylcholine receptor during atherosclerosis progression

(動脈硬化進展におけるアセチルコリン受容体を介した迷走神経の役割)

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Atherosclerosis, a dominant cause of heart attack and stroke, accounts for 85% of deaths due to cardiovascular diseases (CVDs). It is linked to behavioral risk factors such as cigarette smoking, hypertension, and hyperlipidemia. However, the lack of early prevention and detection of CVDs leads to three quarters of the death toll in low- and middle-income countries. Vagus nerve stimulation (VNS) triggers the cholinergic anti-inflammatory pathway (CAP) through the activation of the α7 nicotinic acetylcholine receptor (α7nAChR), and exhibits therapeutic potential in cardiovascular diseases. However, there is still no evidence showing the effects of VNS on atherogenesis. In this study, I showed that GTS-21, an α7nAChR agonist, reduces the expression of *ITGAL*, *ITGA4*, and *SELPLG* in the human monocytic cell line U-937. This effect was proved to be mediated by the downregulation of runt-related transcription factor 3 (*RUNX3*), a transcriptional regulator of *ITGAL* and *ITGA4*. With respect to endothelial cells, GTS-21 reduces the expression of *ICAM-1* and *VCAM-1* in human umbilical vein endothelial cells (HUVECs) involving the lncRNA, small nucleolar RNA host genes 9 (*SNHG9*). *SNHG9* knockdown in HUVECs reduces adhesion and protects cells from the dysfunction induced by TNFα. In the *in vivo* experiment, long-term VNS reduced the plasma lipid content of apolipoprotein E (ApoE)-KO mice compared to the sham group; however, increased atherosclerotic plaque formation was observed in the group undergoing long-term VNS. In conclusion, a novel mechanism of α7nAChR-mediated amelioration of atherosclerosis in both monocytes and endothelial models was revealed; however, VNS *in vivo* showed adverse effects on atherosclerosis.