Transcutaneous Auricular Vagus Nerve Stimulation Exerts Antidepressant Effects by Inhibiting Hippocampal Cell Ferroptosis and Enhancing Neuroplasticity via NRF2 Mediation

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Abstract

Depression is a severe mental disorder characterized by complex pathophysiological changes. Although transcutaneous auricular vagus nerve stimulation (taVNS) has shown therapeutic effects, the underlying mechanisms related to hippocampal oxidative stress and iron dyshomeostasis are still not well understood. This study aimed to investigate whether taVNS exerts antidepressant-like effects by regulating Nrf2-related signaling to inhibit iron dyshomeostasis and enhance hippocampal neuroplasticity. Adolescent rats were randomly divided into control, model, taVNS, taVNS+DMSO, taVNS+ML385 (Nrf2 inhibitor), and taVNS+EX527 (Sirt1 inhibitor) groups. Except for the control group, the remaining rats were subjected to chronic unpredictable mild stress (CUMS). The intervention groups received 21-day taVNS treatment and were intraperitoneally injected with inhibitors prior to each stimulation session. Behavioral assessments (SPT, OFT, EPM) were carried out both before and after the intervention. Hippocampal tissues were collected at PND 80 for Western blot (WB) and immunofluorescence (IF) analysis. Our results showed that CUMS induced significant depressive and anxiety-like behaviors. taVNS significantly alleviated these behavioral abnormalities, and there was no significant difference between the taVNS and taVNS+DMSO groups. However, ML385 or EX527 significantly blocked these therapeutic effects. At the molecular level, taVNS upregulated the expression of Sirt1, Nrf2 and GPX4, while downregulating the expression of Keap1 and GSDMD. These regulatory effects were consistent between the taVNS and taVNS+DMSO groups, yet were significantly reversed by ML385 or EX527. Immunofluorescence results indicated that taVNS reduced the number of Iba-1-positive cells and the fluorescence intensity of 4-hydroxynonenal (4-HNE), while increasing the signals of NeuN, PSD95, MAP2, BDNF, and TREM2 in the CA1, CA3, and DG regions. Similarly, these histological improvements were consistent between the taVNS and taVNS+DMSO groups but were significantly blocked by ML385 or EX527. In conclusion, these findings imply that taVNS exerts antidepressant-like effects by inhibiting hippocampal iron dyshomeostasis, alleviating neuroimmune dysregulation, and enhancing neuroplasticity, a process predominantly mediated by the Nrf2 signaling pathway.

Keywords

Transcutaneous Auricular Vagus Nerve Stimulation, Depression, Ferroptosis, NRF2, Hippocampus