NO-ergic mechanisms of age-related changes in the sensitivity of lymphatic vessels to photobiomodulation

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Photobiomodulation (PBM) is a promising noninvasive therapy for brain diseases. One of the therapeutic mechanisms is the stimulation of brain drainage and clearance by enhancing the function of the lymphatic vessels involved in these processes. However, sensitivity to PBM is known to decrease with age. The mechanisms behind this phenomenon remain poorly understood. PBM exerts its therapeutic effects largely by stimulating nitric oxide (NO) production in the endothelium of blood vessels and neurons. Based on this fact, it has been hypothesized that PBM's stimulating effects on lymphatic vessel function are also associated with PBM-mediated increases in NO production in the lymphatic endothelium and that this process slows with age, which may explain the decreased sensitivity to PBM in older individuals.The aim of this study was to investigate age-related differences in the NO-ergic mechanisms of PBM effects on the contractility of afferent (drainage function) and efferent (filtration function) cervical lymphatic vessels (cLVs) and their relationship to brain clearance.

The study was performed on male BALB/c mice aged 3, 12, and 24 months. PBM (1050 nm LED, 10 J/cm²) was applied. cLV contractility was assessed in vivo using two-photon microscopy and optical coherence tomography (OCT). NO production was measured in primary cultures of lymphatic endothelial cells (LECs) in vitro. The NO synthase inhibitor L-NAME was used for NO blockade. Lymphatic clearance of amyloid-beta (Aβ) from the brain to deep cervical lymph nodes (dcLNs) was evaluated by confocal microscopy, and cLV morphology was also analyzed.

The results showed that PBM significantly increased the contractility of both afferent and efferent cLVs as well as NO production in LECs in 3- and 12-month-old mice, and these effects were suppressed by L-NAME. In contrast, 24-month-old mice exhibited reduced basal cLV contractility, no significant increase in cLV contractility or NO production after PBM, insensitivity to NO blockade, reduced lymphatic clearance of Aβ from the brain, and lymphatic hyperplasia (increased LYVE-1 signal) in dcLNs.

Thus, aging leads to lymphatic endothelial dysfunction characterized by reduced basal NO production, impaired cLV contractility, and morphological changes, which together cause resistance to PBM. The NO-ergic pathway is essential for PBM-induced stimulation of brain lymphatic drainage in young and middle-aged mice but is compromised in aged animals. These findings suggest that combined therapy including PBM and NO enhancement may improve the effectiveness of treatment for brain diseases in the elderly.

Keywords: photobiomodulation, aging, nitric oxide, lymphatic drainage, cervical lymphatic vessels, brain clearance, Alzheimer's disease.

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