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Astrovascular dysfunction and aberrant submembrane hemoglobin in erythrocytes drive cerebral hypoxia in Alzheimer's disease

Academic supervisor – Brazhe Nadezda Aleksandrovna

Xu Yu
Postgraduate
Lomonosov Moscow State University, Биологический факультет, Кафедра биофизики, Moscow, Россия
E-mail: xyhhh1997@163.com

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by the neurofibrillary tau tangles and amyloid β (Aβ) plaques accumulation in the brain with growing cognitive decline. New evidence suggests that cerebral hypoxia plays a key role in AD, which remaining elusive. Here, using *in vivo* Raman spectroscopy in transgenetic AD mice, we uncovered impaired arteriolar vasomotion and reduced cerebral oxygen extraction in reponse to physiological stimulation. Given the critical role of cellular energy metabolism and nitric oxide signaling in neuro-astro-vascular coupling, we next measured the mitochondrial redox states in neurons and astrocytes, and found that there were different redox responses to the stimulation in both cell types across AD stages, suggesting a changeable redox state that could potentially affect the electron supply for NO reduction from nitrite in the mitochondrial respiratory chain (ETC). Notably, we observed a decrease of relatived amount of reduced cytochromes within astrocytic mitochondrial ETC in the quiescence state under the symptomatic AD stage. Furthermore, using surface-enhanced Raman spectroscopy with microcavity-based substrates, we revealed the alterations in submembrane hemoglobin proportions and function in the erythrocytes as the disease progresses, which may lead to the diminished oxygen extraction and cerebral hypoxia. Together, our findings revealed that the a multi-level mechanism underlying cerebral hypoxia in AD, encompassing dysregulated mitochondrial redox states in both neurons and astrocytes, impaired neurovascular function, and abnormal oxygen-carrying capacity of erythrocytes. These findings highlight novel, integrated targets for intervening in AD progression.

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