Therapeutic Inhibition of Phosphodiesterase 2A2 Ameliorates Mitochondrial Dysfunction and Cognitive Decline in Alzheimer's Disease

Ying Xu, Ph.D.

Department of Anesthesiology, Rutgers, The State University of New Jersey Newark, NJ USA

Phosphodiesterases (PDEs) are a superfamily of enzymes responsible for the hydrolysis of cAMP and cGMP, second messengers that regulate important cellular functions. Among PDE family members, PDE2A is the most prevalently expressed PDE in the frontal cortex and hippocampus, which are vulnerable to the development of AD. Our studies demonstrated that increased expression of PDE2A was found in the brain of AD patients and animal models accompanied by impaired cAMP/cGMP signaling and *in vitro* studies, which suggest a critical role of aberrant PDE2A signaling in mediating Aβ-induced mitochondrial dysfunction and neuronal dysfunction. Moreover, PDE2A overexpression impaired mitochondrial function accompanied by extensive mitochondrial fragmentation. Aβ-induced mitochondrial fragmentation and respiratory deficits were rescued by a PDE2A inhibitor, further suggesting mitochondrial dynamics and function could be mechanism of action for PDE2A to influence cognition. In addition, novel animal models with PDE2A conditional knockout in the forebrain were crossed with different AD transgenic mouse models and carefully characterized. Considering that PDE2A2 isoform uniquely localized to mitochondria, the learning and memory behavior was determined by microinjection of AAV-PDE2A2-shRNA to the CA1 of hippocampus in mice. The role of PDE2A2 in brain function and behavior in AD mouse models were also determined using functional PDE2A knockout mice. Our studies provide mechanistic insights into molecular mechanisms underlying mitochondrial dysfunction in AD.

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Presenter Name and Contact Information:
Ying Xu, MD, PhD
Department of Anesthesiology
Rutgers, The State University of New Jersey
Newark, NJ 07103
Phone: 973-972-6890
Email: yx328@njms.rutgers.edu