

Psychiatry and Neuroscience Seminar Series 2025



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Astrocyte-to-neuron H₂O₂ signaling provides a new framework for investigating the origin of Alzheimer's disease

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Room D Levy, 102-108 rue de la santé - 75014 Paris

Alzheimer's disease (AD) is a progressive neurodegenerative condition characterized by memory impairments and dementia. This complex disease includes a long asymptomatic phase. In addition to amyloid beta and TAU pathologies, AD is linked to early defects in brain energy metabolism and redox homeostasis. Over the past decade, our laboratory has conducted an extensive study of the interplay between brain energy metabolism and memory, utilizing *Drosophila* as a model organism. In view of these findings, we have recently undertaken research into the potential links between brain energy metabolism and AD molecular and cellular dysfunctions.

Astrocytes interact with neurons during cognitive processes. Especially, astrocytes help neurons fight oxidative stress, a needed function since active neurons are prone to reactive oxygen species (ROS) damage. ROS also play major physiological functions, but it remains unknown how neuronal ROS signaling is activated during memory formation and if astrocytes play a role in that process. We discovered an astrocyte-to-neuron H₂O₂ signaling (ANHOS) cascade essential for long-term memory formation. This mechanism, revealed by *in vivo* H₂O₂ imaging using an ultrasensitive sensor, involves the local synthesis of beneficial ROS by astrocytic enzymes. Notably, Amyloid Precursor Protein plays a central role in the ANHOS cascade via its extracellular Cu²⁺-binding E2 domain. Conversely, A β hinders ANHOS by interacting with a major molecular target, the alpha-7 acetylcholine receptor, expressed in astrocytes. Lastly, I will present preliminary findings suggesting that the expression in astrocytes of APOE4, the major genetic risk factor in AD, also impairs ANHOS.

Our discovery unveils a novel mechanism of neuronal plasticity essential for long-term memory formation. It opens the intriguing possibility that, in humans, AD synaptic defects may be initially linked to a deficiency of beneficial ROS crucial for memory formation, with the observed oxidative stress in AD being a secondary effect.