Presentation Abstract

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Presentation Title: Novel heteroaromatic organic compound normalized calcium abnormalities in α-synuclein transgenic Parkinson’s Disease-like mice model

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Abstract: Abnormal accumulation of α-synuclein is central to the pathogenesis of many disorders with Parkinsonism and dementia. Recently, using in vivo two-photon laser scanning microscopy, we demonstrated that neurons in the somatosensory cortex of transgenic mice expressing wild-type human α-synuclein exhibit pathological calcium activity. The most evident pathology was observed in response to repetitive stimulation - when subsequent stimuli were presented before the calcium signal returned to baseline - and was characterized by augmented, long-lasting calcium transients with considerable deviation from the exponential decay. These alterations were detected in the absence of a significant increase in neuronal spiking response, consistent with the hypothesis that α-synuclein promotes calcium alterations via interference with intrinsic cellular calcium buffering mechanisms. In the present study, we used this augmented calcium response as an in vivo functional biomarker of pathology and explored the therapeutic potential of a novel α-synuclein stabilizing agent: heteroaromatic organic compound-01 (HAOC-01). HAOC-01 was designed to bind the hydrophobic NAC domain of α-synuclein and to alter α-synuclein
monomer structure, preventing binding of the α-synuclein monomer to cellular membranes and other α-synuclein molecules. The drug was administered acutely during an imaging session by intracortical microinjection. We established the pretreatment baseline in each α-synuclein transgenic mouse by imaging calcium activity in individual cortical neurons in response to a train of 3 sensory stimuli delivered at 3 Hz (electrical whisker stimulation, 1 mA). Calcium measurements were repeated in the same neurons every ~15 min, while HAOC-01 (10 µM) was microinjected into the cortical tissue within the imaged area for 100 ms, 2 s prior to each sensory stimulus delivery. In agreement with our previous data, pre-treated neuronal calcium transients were characterized by an abnormal increase in the amplitude in response to each consecutive stimulus in the train. Administration of HAOC-01 reversed the pathological augmentation in the calcium response ~1 h after the beginning of microinjections. The effect was specific to HAOC-01 because vehicle-treated transgenic mice exhibited no improvement. These results suggest that synuclein-stabilizing agents may normalize α-synuclein-related changes in calcium homeostasis.

Disclosures:  

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