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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 pre-treatment 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.

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