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Presentation Abstract

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Title: In vivo study of abnormal neuronal $Ca^{2+}$ activity in α-synuclein transgenic mice model of Parkinson's disease using 2-photon microscopy

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Abstract: Although significant progress has been made in understanding molecular mechanism of Parkinson's disease, translation of these findings into clinically effective treatments remains a major challenge today. On the molecular level, it has been recently shown that α-synuclein (α-syn) might form channel-like oligomers that lead to an increase in intracellular $Ca^{2+}$ in cell culture and *in vitro* assays. In this context, the central hypothesis of this study was that α-syn dysregulates neuronal $Ca^{2+}$ homeostasis *in vivo*.
To test this hypothesis, 2-photon microscopy has been utilized to assess neuronal $Ca^{2+}$ activity *in vivo* in transgenic (tg) mice expressing human α-syn under the mThy-1 promoter. Neuronal response to a sensory stimulus (electrical whisker stimulation, 0.3-1 mA, 100 μsec, a single pulse or 1-sec train at 10 Hz) was mapped using surface potential recordings with a silver ball electrode. Following the mapping, a mixture of calcium dye Oregon Green BAPTA-1 (OGB) AM and astrocytic marker SR101 were pressure injected 500 μm below the cortical surface at the center of the neuronal response. $Ca^{2+}$ activity in neurons at depths of 150 and 250 μm was imaged in 1 year old α-syn tg mice (fully developed disease) and compared to age-matched WT littermates ("controls").

We imaged stimulus-evoked $Ca^{2+}$ activity in 5 and 5 tg and control mice, respectively. In 85% of the tg neurons (n=216 at 150 μm and n=213 at 250 μm), stimulus-evoked $Ca^{2+}$ responses were characterized by an increase in peak amplitude. In this population, trial-averaged $Ca^{2+}$ response amplitude was up to 190% and 145% relative to the mean control responses at 150 μm and 250 μm, respectively (n=206 at 150 μm and n=164 at 250 μm). In addition, prolonged $Ca^{2+}$ decays were detected in 28% of the imaged tg neurons after the termination of the stimulus. This was assessed by fitting the decay with an exponential function $y=ae^{-x/\tau}$, where y - change in fluorescence of OGB, x - time, a and τ - constants. The fitted time constant τ indicated significantly longer decays in tg neurons imaged at the depth of 150 μm (up to 150% vs. controls). No significant difference in τ was evident in neurons imaged at 250 μm. These results imply an increase in $Ca^{2+}$ entry and slow clearance of the excess of $Ca^{2+}$ in tg neurons. Further studies will be required to address the mechanisms through which α-syn provokes neuronal $Ca^{2+}$ dysregulation.

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CALCIUM IMAGING

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