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Molecular and cell biology: Tau-related mechanisms

Synaptic stimulation protects against pathological tau by enhancing lysosomal degradation

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Abstract

Background: Changes in synaptic excitability and reduced brain metabolism are among the earliest alterations associated with the development of Alzheimer's disease (AD) (Reiman et al., 2004; Sperling et al., 2009). Among different approaches for therapeutics, the stimulation of synaptic activity has been shown to be protective in models of AD, and deep brain stimulation (DBS) provides amelioration in AD patients (Sankar et al., 2015; Swaab and Bao, 2010; Tampellini, 2015). Such positive effects might reflect changes occurring at cellular levels when activity is induced, indicating that brain stimulation might promote cellular mechanisms correcting neuronal and synaptic dysfunctions. We have demonstrated that synaptic stimulation, via DBS or other methods, exerts protection in mouse models of AD and frontotemporal *dementia* (FTD) by enhancing autophagy, lysosomal degradation of pathologic tau, and protecting synapses (Akwa et al., 2018; Mann et al., 2018). Ongoing investigations are revealing the involvement of TFEB and its downstream genes in the enhancement of lysosomal activity upon stimulation.

Method: Synaptic activity was induced by electrode implantation in the entorhinal cortex of 3xTg mice (Mann et al., 2018). Cultured neurons were prepared from E15 PS19 mouse embryos (Akwa et al., 2018) and stimulated at 14 days *in vitro* (Ehlers, 2003). RT-qPCR was performed as described (Napolitano et al., 2018). Confocal immunofluorescence, Western blot and statistical analyses were performed as described (Akwa et al., 2018).

Result: DBS was able to reduce levels of hyperphosphorylated and oligomeric (but not total) tau restoring levels of synaptic proteins back to wild-type in 3xTg mice. Pathological tau clearance required lysosmal activity, which was enhanced by synaptic stimulation. Trascription factor EB (TFEB) (Sardiello et al., 2009) plays a pivotal role in regulating lysosomal biogenesis and autophagy, and is involved in activity-driven tau degradation. Indeed, our recent RT-qPCR data analyses revealed increase expressions of TFEB

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downstream genes, including ATP6-V1H and ATP6-V0D1, in neurons during synaptic stimulation.

Conclusion: The enhancement of lysosomal degradation by the involvement TFEB and related genes demonstrated positive effects of DBS/synaptic stimulation at cellular and molecular level against pathological tau.