LTD-inducing low frequency stimulation enhances p-Tau181 and p-Tau217 in an age-dependent manner in live rats

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Abstract

Background: The progressive cognitive decline in Alzheimer’s disease (AD) patients correlates with the extent of tau pathology, in particular tau hyperphosphorylation, which is strongly age-associated. Although elevation of phosphorylated tau (p-Tau) on residues Thr181 (p-Tau181), Thr217 (p-Tau217), and Thr231 (p-Tau231) in cerebrospinal fluid or blood are recently proposed to be particularly sensitive markers of early Alzheimer’s disease (AD), the generation of p-Tau during brain activity is poorly understood. A major form of synaptic plasticity, long-term depression (LTD), has recently been linked to the enhancement of tau phosphorylation. It is still unknown whether the expression levels of p-Tau181, p-Tau217, and p-Tau231 can be enhanced by physiological LTD induction.

Method: Young adult (2-3-months) and aged (17-18-months) male Sprague Dawley rats were used in all experiments. Prior to the surgery, animals were anesthetized with urethane (1.5-1.6 g/kg, i.p.). Field excitatory postsynaptic potentials (EPSPs) were recorded from the stratum radiatum in the CA1 area of left or right hippocampus in response to stimulation of the Schaffer collateral-commissural pathway. LTD was induced using 1 Hz low frequency stimulation (LFS) consisting of 900 pulses (0.2 ms duration). The rats were sacrificed 30 min post-LFS. The expression levels of p-Tau181, p-Tau217, and p-Tau202/205, p-Tau396, and total tau were analyzed using western blotting and immunofluorescent staining.

Result: Here we show that LFS, used to induce LTD, enhances p-Tau181 and p-Tau217 in an age-dependent manner in the hippocampus of live rats. In contrast, phosphorylation at residues Thr231, Ser202/Thr205, and Ser396 is less sensitive to LFS. Further, blocking either NMDARs or mGluR5 strongly inhibits the elevation of both p-Tau181 and p-Tau217. Finally, targeting ageing with a small molecule cognitive enhancer ISRIB (trans-isomer) prevents the increase of both p-Tau181 and p-Tau217 by LFS in aged rats.

Conclusion: Our data provide an in vivo means to uncover brain plasticity-related cellular and molecular processes of tau phosphorylation in health and ageing conditions.