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Pseudohyperphosphorylation of tau is sufficient to induce aberrant sprouting and activation of ERK1/2 in transgenic mice

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Hyperphosphorylation of tau is a characteristic of Alzheimer's disease (AD). Our group has established a model for tau hyperphosphorylation by mutating 10 residues from Ser/Thr to Glu to simulate the negative charge of phosphorylated residues ("pseudohyperphosphorylated (PHP)-tau").

In order to analyze temporal and spatial effects of hyperphosphorylation of tau in a systemic context, we have established transgenic mouse lines that express human wild-type (wt)- or PHP-tau under the control of the CamKIIalpha-promoter that leads to a forebrain specific moderate expression in neurons, i.e. the region where also taupathology in AD is abundant.

For the evaluation of tau-induced changes in the transgenic mice, we quantified spine densities in the neocortex and hippocampus of transgenic mice. The spine densitiy was significantly increased in PHP-tau compared to wt-tau expressing mice. It is known that AD is associated with aberrant pre- and postsynaptic sprouting. Axonal sprouting is also observed in transgenic mice expressing mutated amyloid precursor protein (APP), which suggests that Abeta plays a significant role in this process.

We deduce from our results, that (pseudo)-hyperphosphorylation of tau is sufficient to induce aberrant sprouting in the absence of Abeta. Analyses whether this sprouting is induced by pre- or postsynaptic changes and if functionally active synapses are formed are in progress. It will be interesting to determine if stabilization of these newly formed synapses slows or – in contrary – accelerates the progression of the disease.

Sprouting as observed in our PHP-tau expressing mice is part of neuronal differentiation. One family of enzymes that is involved in cell differentiation are mitogen-acitvated protein kinases (MAPK). Western blot analysis was performed with brain lysates from transgenic mice to check whether PHP-tau induced sprouting is associated with MAPK activation. In fact, we also observed an increased activation of the MAPK ERK1/2 evident by phosphorylation of the residues Thr202 and Tyr204.

ERK1/2 is also known to phosphorylate tau at sites characteristic for AD. Our results suggest the presence of a vicious circle by which (pseudo)-hyperphosphorylated tau activates ERK1/2 which in turn phosphorylates tau.