J Mol Neurosci (2011) 45:432–437
DOI 10.1007/s12031-011-9604-5

Reversibility of Tau-Related Cognitive Defects in a Regulatable FTD Mouse Model

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Received: 20 April 2011 / Accepted: 18 July 2011 / Published online: 6 August 2011

Abstract The accumulation of proteins such as Tau is a hallmark of several neurodegenerative diseases, e.g., frontotemporal dementia (FTD). So far, many mouse models of tauopathies have been generated by the use of mutated or truncated human Tau isoforms in order to enhance the amyloidogenic character of Tau and to mimic pathological processes similar to those in FTD patients. Our inducible mice express the repeat domain of human Tau (Tau_{RD}) carrying the FTDP-17 mutation ΔK280 in a "pro-aggregant" and an "anti-aggregant" version. Based on the enhanced tendency of Tau to aggregate, only the "pro-aggregant" Tau_{RD} mice develop Tau pathology (hyperphosphorylation, coassembly of human and mouse Tau, synaptic loss, and neuronal degeneration). We have now carried out behavioral and electrophysiological analyses showing that only the pro-aggregant Tau_{RD} mice have impaired learning/memory and a distinct loss of LTP. Remarkably, after suppressing the pro-aggregant human Tau_{RD}, memory and LTP recover, while neuronal loss persists. Aggregates persist as well but change their composition from mixed human/mouse to mouse Tau only. The rescue of cognition and synaptic plasticity is explained by a partial recovery of spine synapses in the hippocampus. These results indicate a tight relationship between the amyloidogenic character of Tau and brain malfunction, and suggest that the cognitive impairment is caused by toxic human Tau_{RD} species rather than by mouse Tau aggregates.

Keywords Frontotemporal dementia · Tau · Aggregation · Transgenic mouse models · Tauopathy

Abbreviations

AD	Alzheimer's disease
CBD	Corticobasal degeneration
DOX	Doxycycline
EPSP	Excitatory postsynaptic potential
FTD	Frontotemporal dementia
FTDP-17	Frontotemporal dementia with Parkinsonism linked to chromosome 17
LTP	Long-term potentiation
MARK	Microtubule affinity regulating kinase
Mf	mossy fiber
NFTs	Neurofibrillary tangles
NMDAR	NMDA receptor
PHFs	Paired helical filaments
PiD	Pick's disease
PSP	Progressive supranuclear palsy
Tau_{RD}	Repeat domain of human Tau

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Introduction

A subset of frontotemporal dementias (FTD), such as Pick's disease (PiD), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17), is characterized by the aggregation of the intracellular microtubule-associated protein Tau (tauopathies; Josephs 2008). Further hallmarks of FTD are the degeneration of hippocampal and cortical neurons, progressive behavioral changes, and/or selective language difficulties (Frisoni et al. 1999; Laakso et al. 2000; Josephs 2008). To date, several Tau-transgenic animal models have been generated, expressing mutated or truncated human Tau isoforms, to enhance the amyloidogenic character of Tau and to mimic pathological processes similar to FTD patients (for review, see Götz and Ittner 2008). These models allow one to study tauopathies in living organisms and to understand the interplay of key molecules relevant in the pathogenesis of neurodegenerative diseases; a basic requirement for the development of therapeutic compounds and therapies.

We have generated two types of regulatable transgenic mouse strains expressing the repeat domain of the human Tau (Tau_{RD}) in a pro-aggregant and an anti-aggregant version (Mocanu et al. 2008). The pro-aggregant mutant carries the FTDP17-mutation ΔK280 (van Swieten et al. 2007) which lies within the hexapeptide motif of repeat 2 that promotes the formation of β-structure and the aggregation of Tau (Tau_{RD}/ΔK280; Barghorn et al. 2000). By contrast, the anti-aggregant mutant includes, beside the FTDP17-mutation ΔK280, two additional point mutations Ile to Pro within both amyloidogenic hexapeptide motifs in R2 and R3, which act as β-structure breakers and prevent Tau aggregation (Tau_{RD}/ΔK280/2P; Khlistunova et al. 2006). The expression of Tau_{RD} and the reporter gene luciferase in the responder lines is controlled by a bidirectional promoter in a doxycycline-dependent manner (Tet OFF-system; Gossen and Bujard 2002), such that expression occurs only when doxycycline is absent, and can be switched off by adding doxycycline to the drinking water. Crossing the pro- or anti-aggregant mouse strain with the CaMKIIα-tTA line (activator line; Mayford et al. 1996) leads to transgene expression in the entorhinal cortex and hippocampus, brain regions affected in AD and FTD (Laakso et al. 2000). The use of the reporter protein luciferase allows us to quantify the expression of Tau_{RD} by the luciferase reporter assay in living, double transgenic pro- and anti-aggregant Tau_{RD} mice and to distinguish mice with different levels Tau_{RD} expression (Mocanu et al. 2008; Sydow et al. 2011). Histopathological, biochemical, and electron microscopical analyses demonstrated that pronounced Tau pathology occurs only in pro-aggregant Tau_{RD} mice, e.g., Tau phosphorylation at several diagnostic sites, Tau missorting into the somatodendritic compartment, co-aggregation of human and endogenous mouse Tau, synaptic and neuronal loss, and astrogliosis. By contrast, the anti-aggregant mutant Tau_{RD} mice do not develop a FTD-like phenotype (Mocanu et al. 2008). This argues strongly that the pathology is related to the β-propensity of Tau and not to other properties of Tau such as microtubule stabilization which is similar for pro- and anti-aggregant Tau_{RD}.

The extent of aggregation depends on the expression level of pro-aggregant Tau_{RD} (Sydow et al. 2011), indicating that an overexpression of Tau (mutated human Tau or non-mutated endogenous mouse Tau) induces the formation of pre-tangles stages or NFTs, as observed in other models (SantaCruz et al. 2005; Adams et al. 2009). It is possible that the expression of pro-aggregant Tau_{RD} leads to cell events which modify the endogenous mouse Tau as well (e.g., phosphorylation and conformational changes), enhance the amyloidogenic character of the endogenous mouse Tau, and thus promote the co-aggregation of human and mouse Tau within neurons (Fig. 3; see also Sydow and Mandelkow 2010). To explain the spreading of pathological Tau within the brain of AD patients and patients with other neurodegenerative diseases (Braak and Braak 1991), it has been proposed that toxic species of amyloidogenic proteins propagate their conformation to "healthy" variants of endogenous proteins in other cells in a "prion-like" fashion (Frost and Diamond 2010; Clavaguera et al. 2009), possibly via the exocytosis and re-uptake of oligomeric species.

To demonstrate the relation between Tau pathology, synaptic loss, and cognitive impairment, we have checked our pro- and anti-aggregant Tau_{RD} mice in behavioral and electrophysiological studies. The results show that only the amyloidogenic pro-aggregant Tau_{RD} causes learning/memory impairment and a distinct reduction in the synaptic plasticity compared to the anti-aggregant Tau_{RD} (Sydow et al. 2011). Under switch-off conditions, neuronal loss and tangles of mouse Tau persist, but synaptic plasticity and cognition are rescued in the pro-aggregant OFF mice, presumably due to the recovery of synapses. This indicates that the amyloidogenic pro-aggregant Tau_{RD}/ΔK280 induces toxic mechanisms that are reversible after the removal of the amyloidogenic pro-aggregant Tau_{RD} from the cells.

Results and Discussion

For the mouse models used here (Mocanu et al. 2008), we have chosen the CaMKIIα promoter in order to avoid the transgene expression in the motor neurons. This circumvents a neuromotor phenotype caused by axonal transport inhibition due to elevated Tau which has been observed in

transgenic mouse models employing other promoters and resulting in motor deficits (Spittaels et al. 1999; Lewis et al. 2000; Schindowski et al. 2006; Yoshiyama et al. 2007). This enabled us to determine learning and spatial memory of our transgenic mice in the Morris water maze (Morris 1984). The pro-aggregant Tau_{RD}/ΔK280 mice at 10 months' expression showed a slower rate of learning on the second and third day of acquisition, compared to anti-aggregant and control mice (Sydow et al. 2011). An analogous impact of Tau on learning and memory has been observed for other Tau transgenic mouse models (for review, see Denk and Wade-Martins 2009; Ittner and Götz 2011). More extended expression of the pro-aggregant Tau_{RD} (14 months) causes severe deficits in learning and memory in a reversal Morris water maze, while switching off the pro-aggregant Tau_{RD}/ΔK280 expression for ~4 months (10 months ON plus 4 months OFF) rescues the cognitive impairment, comparable to anti-aggregant ON/OFF and control mice (Fig.1a).

These behavioral findings were confirmed by the passive avoidance task. It indicates for the pro-aggregant ON mice at 14 months' expression a poor memory retention, whereas the pro-aggregant OFF mice (10 months ON plus 4 months OFF) were comparable to control and anti-aggregant ON and OFF mice (Fig. 1b). Similar results were found for another inducible mouse model rTg4510 that developed cognitive impairments upon expression of Tau-P301L (another FTD mutation within the repeat domain of Tau), which could be rescued after switch off (SantaCruz et al. 2005; Ramsden et al. 2005). In our pro-aggregant Tau_{RD}/ΔK280 mice, the measurements of the NMDAR-independent LTP of the CA3–mossy fiber synapses indicated a reduction of synaptic plasticity, followed by a reversal to control levels after switch off (Fig. 1c). These observations are comparable to LTP studies of other Tau transgenic mice (Oddo et al. 2003; Yoshiyama et al. 2007; Rosenmann et al. 2008; Polydoro et al. 2009) and measurements of the excitatory synaptic transmission in primary neurons of rTg4510 mice (Hoover et al. 2010), showing a Tau-dependent reduction of the synaptic plasticity. Some authors have argued that synapses are damaged by soluble Tau species rather than by Tau aggregates since in several mouse models the synaptic decay precedes the Tau aggregation (Eckermann et al. 2007; Yoshiyama et al. 2007; Kimura et al. 2010); however, the nature of soluble pre-fibrillar Tau oligomers remains ill-defined.

Based on our results, the question arises how learning and memory is rescued again in pro-aggregant mice after the exogenous Tau has been switched off. Histopathological analyses of the pro-aggregant OFF mice by Gallyas silver staining for neurofibrillary tangles (Gallyas 1971; Braak et al. 1994) and NeuN staining for neuronal cell bodies as well as biochemical studies by sarcosyl

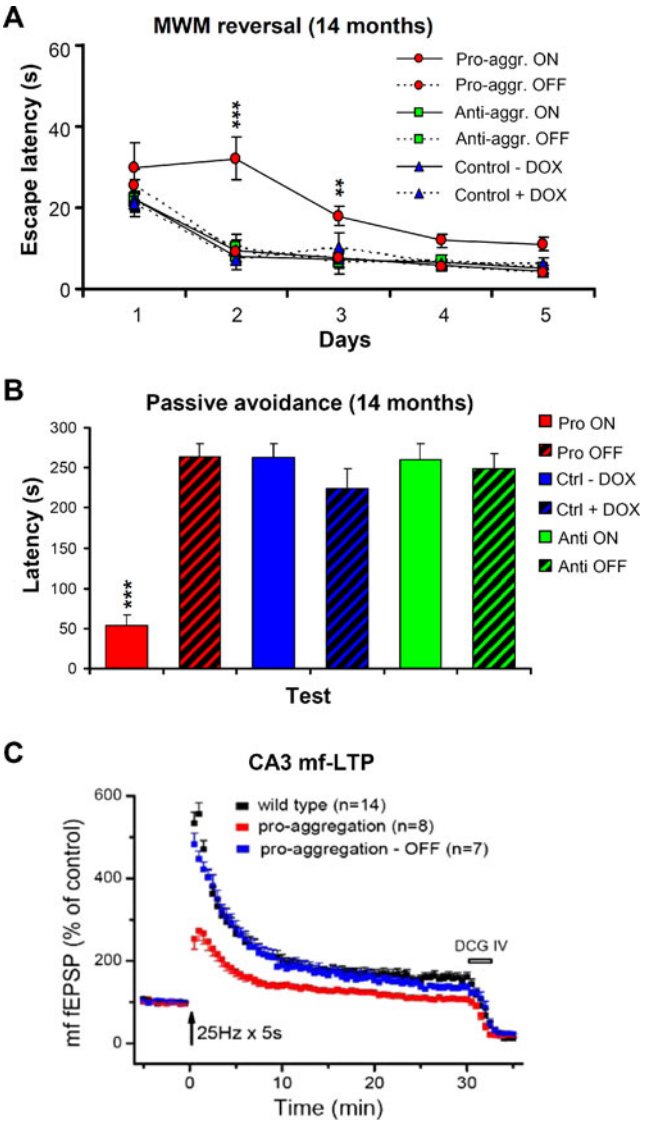

Fig. 1 Recovery of learning, memory, and synaptic plasticity after switching off the expression of pro-aggregant Tau_{RD} with FTD-mutation ΔK280. **a** Switching off the pro-aggregant Tau_{RD}-expression for 4 months rescues the cognitive impairment in the pro-aggregant OFF mice (*red*, *dashed line*), comparable to control (*blue full and dashed lines*) and anti-aggregant ON and OFF mice (*green full and dashed lines*). By contrast, the pro-aggregant ON mice which continued their Tau_{RD} expression showed progressive cognitive impairment (*red*, *full line*). **b** The passive avoidance task demonstrates an impaired memory retention for the pro-aggregant ON mice (14 months ON, *red bar*), whereas the pro-aggregant OFF mice (10 months ON+4 months OFF, *black and red striped bar*) behave similar to control (*blue and blue and black bars*) and anti-aggregant ON (*green bar*) and OFF (*green and black striped bar*) mice. **c** The summary diagram of fEPSP measurements demonstrates the complete reversal of LTP suppression in the pro-aggregant OFF mice (*blue squares*) back to control level (*black squares*), while the pro-aggregant ON mice show distinctly reduced synaptic plasticity (*red squares*). All data are means ± SEM. *Asterisks* in (**a**) and (**b**) indicate the significance of differences between PRO-ON versus PRO-OFF, ANTI-ON, ANTI-OFF, and CTRL mice (**$P<0.01$, ***$P<0.001$). *Aggr.* aggregant, *Ctrl* control, *DOX* doxycycline, *mf* mossy fiber, *LTP* long-term potentiation (reprinted from Sydow et al. 2011, with permission)

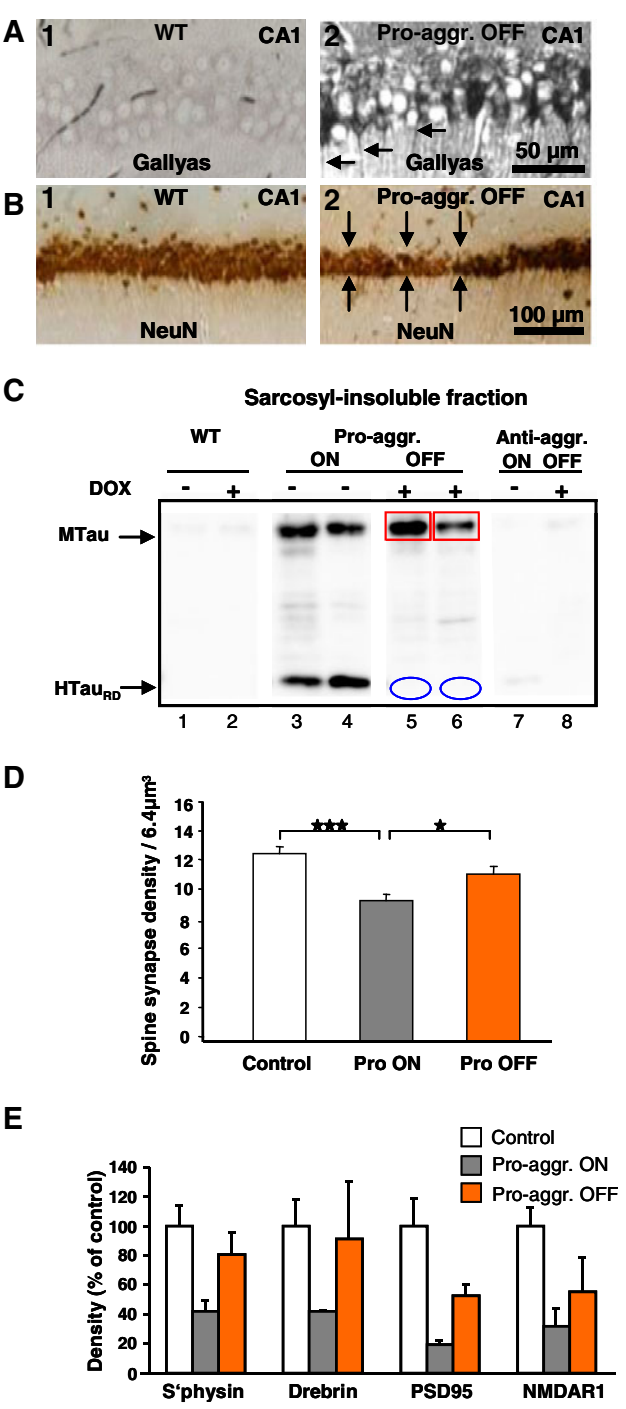

Fig. 2 Mouse Tau aggregates and neuronal loss persist in the pro-aggregant Tau$_{RD}$ OFF mice, but the synapses partly recover. **a**–**b** Pro-aggregant Tau$_{RD}$ OFF mice still have Tau aggregates (**a**, *2*; Gallyas silver positive hippocampal neurons; *arrows*) and neuronal loss in the CA1 region (**b**, *2*) determined by NeuN staining (*arrows*), compared to WT mice (**a**, *1*; **b**, *1*). *Scale bars*—**a** *1*, *2*=50 µm; **b** *1*, *2*=100 µm. **c** Western blot analysis of the sarcosyl-insoluble fraction shows in pro-aggregant ON mice (14 months, *lanes 3–4*) a co-aggregation of the exogenous human and the endogenous mouse Tau. Switching the pro-aggregant Tau$_{RD}$ expression on for 10 months and then off for 4 months revealed that the level of aggregated exogenous human Tau$_{RD}$ (sarcosyl-insoluble protein) disappeared (*blue circles*, *lanes 5–6*), but the aggregated endogenous mouse Tau still persists in the sarcosyl-insoluble fraction (*red squares*, *lanes 5–6*). By contrast, neither the controls (*lanes 1–2*) nor anti-aggregant ON (*lane 7*) and anti-aggregant OFF (*lane 8*) mice develop any Tau aggregates. **d** Quantitative evaluation of spine synapses by electron microscopy in the stratum radiatum of the CA1 hippocampal region shows a decrease of synapses after 10 months of pro-aggregant Tau$_{RD}$ expression (*gray bar*) compared to 74% of control (*white bar*). In the case of the pro-aggregant OFF mice (10 months ON +4 months OFF; *orange bar*), the number of spine synapses are rescued to 90% of control, indicating substantial recovery. (*P* values—bar 1/2 *P*=0.000031, bar 2/3 *P*=0.018, bar 1/3 *P*=0.062). **e** Densitometric analysis of western blots for synaptic proteins (synaptophysin, drebrin, PSD95, and NMDAR1), all normalized to β-actin (*n*=4), indicate reduced levels of synaptic proteins to ~40% (*gray bars*) after pro-aggregant Tau$_{RD}$ expression compared to control mice (*white bars*). The *orange bars* show the rescue of synaptic proteins in pro-aggregant OFF mice (10 months ON+4 months OFF) to ~70% compared to control mice. *PSD* postsynaptic density, *S'physin* synaptophysin, *HTau* human Tau, *MTau* mouse Tau, *WT* wild type, *Dox* doxycycline (reprinted from Sydow et al. 2011, with permission)

extraction (Greenberg and Davies 1990) demonstrated that both the Tau aggregates (Fig. 2a, 2; Fig. 2c, lanes 5–6; Fig. 3) and neuronal loss persisted (Fig. 2b, 2). This means that the composition of the co-aggregates containing exogenous and endogenous Tau can be altered when the exogenous toxic human Tau$_{RD}$/ΔK280 disappears from the protein pool (Fig. 3). It is conceivable that a similar beneficial effect could be achieved by low molecular weight brain-penetrant aggregation inhibitors which neutralize the β-propensity of Tau. Such inhibitors are currently under investigation in several laboratories (for review, see Brunden et al. 2009; Bulic et al. 2010).

The evaluation of the synapses by electron microscopy and western blotting indicated a partial recovery of the number of spine synapses and levels of synaptic markers after the removal of the human amyloidogenic Tau$_{RD}$/ΔK280 (Fig. 2d–e). Analogous spine counts for rTg4510 mice excluded Tau aggregates as a source of synaptic decay since hippocampal neurons with and without NFTs showed approximately the same number of dendritic spines (Rocher et al. 2009).

Several conclusions can be drawn from these experiments:

- The expression of the pro-aggregant Tau$_{RD}$/ΔK280 leads to nucleation of Tau aggregates triggered by the highly amyloidogenic exogenous Tau, followed by co-aggregation with endogenous Tau. It is possible that this also induces other cell events (e.g., the activation of kinases, such as MARK), which can "poison" the normal and non-mutated mouse Tau (e.g., phosphorylation or conformational changes), so that the mouse Tau becomes more amyloidogenic. The co-aggregates are in equilibrium with their subunits, and this equilibrium can be shifted when the toxic human Tau$_{RD}$/ΔK280 is switched off, resulting eventually in aggregates of mouse Tau only (Fig. 3).

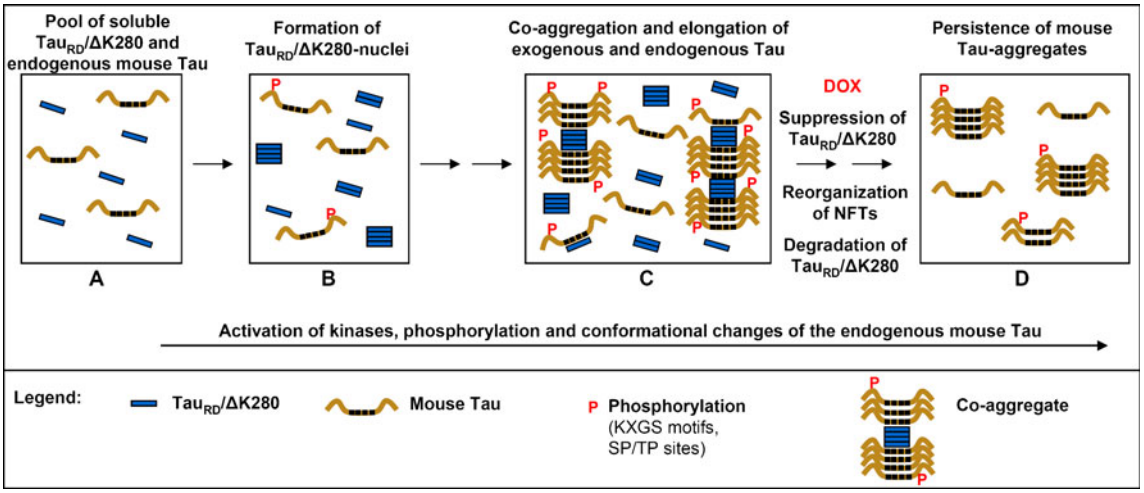

Fig. 3 Model of the co-aggregation in pro-aggregant ON mice and the reorganization of the co-aggregates after switching off the pro-aggregant Tau$_{RD}$ expression. **a** In neurons of pro-aggregant ON mice, the amyloidogenic human Tau$_{RD}$/ΔK280 and endogenous mouse Tau initially coexist in soluble form. **b** Tau$_{RD}$/ΔK280 generates nuclei for aggregation because of its high β-propensity. **c** The nuclei can be elongated both by exogenous and endogenous mouse Tau through interactions of the repeat domains (*dotted black* for mouse Tau). **d** Switching off the pro-aggregant human Tau$_{RD}$ expression leads to a reorganization of the co-aggregates (NFTs) and a degradation of the human pro-aggregant Tau$_{RD}$, while the mouse Tau still continues to form aggregates since it is expressed continuously. *Horizontal arrow*—the aggregation process is accompanied (or preceded) by other cellular events, including the activation of kinases which cause phosphorylation and conformational changes of exogenous and endogenous mouse Tau which may render mouse Tau more amyloidogenic. *Lower box*—legend to symbols

- The progression of the protein aggregation is related to the amount of soluble amyloidogenic protein since the pro-aggregant Tau$_{RD}$ mice show a concentration-dependent formation of Tau aggregates.
- Behavioral deficits correlate with the β-propensity of Tau; thus, only the pro-aggregant mutant mice develop an impaired cognition, while anti-aggregant mutant mice do not.
- After switching off the pro-aggregant Tau$_{RD}$/ΔK280 expression, neuronal loss and aggregates of mouse Tau still persist, but learning/memory and LTP recover. The rescue of behavioral deficits in the pro-aggregant OFF mice is based on the partial recovery of synapses, suggesting that a decay of synapses is caused by soluble toxic pro-aggregant Tau$_{RD}$/ΔK280 species rather than by persistent mouse Tau aggregates.
- The switch OFF situation suggests a possible therapy for the pro-aggregant mice, and the analysis of the pro-aggregant OFF mice opens the way to design new therapies for FTD patients.

A key conclusion of the results presented here is that cognition and synaptic plasticity can be restored in pro-aggregant mice by the recovery of synapses, even though neuronal loss and neurofibrillary tangles (of mouse Tau) persist. Thus, therapeutic approaches could be based on compounds which transform or keep Tau in a non-amyloidogenic conformation to avoid synaptic damage and cognitive decline.

Acknowledgments We thank Dr. A. Haemisch and his team of the animal facility at University of Hamburg Medical School for their continuous help in mouse breeding, Dr. H. Bujard and K. Schoenig (University of Heidelberg) for initial help with inducible transgenic mice, S. Hahn and A. Hofmann for excellent technical assistance, and Dr. A. Marx (Hamburg) for advice on statistics. We gratefully acknowledge reagents from Dr. E. Kandel (Columbia University, New York—CaMKIIα-tTA activator transgenic mice). This research was supported by the Max-Planck-Society, Deutsche Forschungsgemeinschaft (AL 294/9-1 to C.A.), the Bundesministerium für Bildung und Forschung/Kompetenznetz Degenerative Demenzen program (E.-M.M.), the Breuer Foundation (E.-M.M.), EU-FP7/Memosad (Grant Agreement 2006121 to E.-M.M. and R.D.), Fonds Wetenschappelijk Onderzoek (FWO)-Vlaanderen (Grant G.0327.08 to D.B. and R.D., FWOjunior scholarship to A.V.d.J.), the KUL2004 Impulse Program, Interdisciplinair Onderzoek Project 06/004, Onderzoekstoelage 06/23 (D.B.), and a K.U. Leuven fellowship (T.A.).

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