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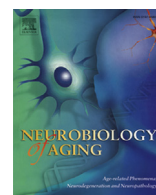
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Hyperexcitability and seizures in the THY-Tau22 mouse model of tauopathy



Victoria Gomez-Murcia^{a,b,#}, Ursula Sandau^{c,#}, Barbara Ferry^d, Sandrine Parrot^d, Cyril Laurent^a, Marie Basquin^a, Luc Buée^a, Detlev Boison^{e,*,#}, David Blum^{a,*,#}

^a University of Lille, Inserm, CHU Lille, U1172 - LiNCog - Lille Neuroscience & Cognition, Lille, France

^b Alzheimer & Tauopathies, LabEx DISTALZ, LiCEND, Lille, France

^c Department of Anesthesiology and Perioperative Medicine, Oregon Health and Sciences University, Portland, OR, USA

^d Centre of Research in Neuroscience Lyon, CNRS UMR 5292 - INSERM U 1028 - Université Claude Bernard Lyon 1, Bron, France

^e Department of Neurosurgery, Robert Wood Johnson Medical School, Rutgers University, Piscataway, NJ, USA

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ABSTRACT

Epileptic seizures constitute a significant comorbidity of Alzheimer's disease (AD), which are recapitulated in transgenic mouse models of amyloidogenesis. Here, we sought to evaluate the potential role of tau pathology regarding seizure occurrence. To this end, we performed intra-hippocampal electroencephalogram (EEG) recordings and PTZ (pentylenetetrazol) seizure threshold tests in THY-Tau22 transgenic mice of AD-like tau pathology. We demonstrate that despite a lack of spontaneous epileptiform activity in Tau22 mice, the animals display increased PTZ-induced seizure susceptibility and mortality. The increased propensity for induced seizures in THY-Tau22 mutants correlates with astrogliosis and increased expression of adenosine kinase, consistent with increased network excitability. These data support an impact of tau pathology toward AD-associated seizures and suggest that tau pathology may contribute to seizure generation in AD independent of A β pathology.

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1. Introduction

The microtubule-associated protein tau is a scaffolding protein, largely expressed by neurons (Arendt et al., 2016). Under pathological conditions, tau undergoes several modifications that are thought to impair brain function and to cause neurodegeneration. Neurofibrillary tangles, made of hyperphosphorylated and aggregated Tau proteins ("Tau pathology") are hallmarks of Alzheimer's disease (AD) and other dementia, particularly some subtypes of frontotemporal lobar degenerations (FTLDs; Lebouvier et al., 2017; Sergeant et al., 2008). In AD, neuronal Tau pathology initially appears at very circumscribed brain regions and subsequently progresses throughout the brain in a fairly predictive stereotypical pattern. Topographical spread of Tau pathology has been linked to

progressive cognitive deterioration (Bejanin et al., 2017; Brier et al., 2016; Colin et al., 2020; Duyckaerts et al., 1997). All these observations support a pivotal contribution of neuronal Tau pathology to cognitive deficits. However, mechanisms underlying neuronal Tau pathology-induced cognitive deficits in AD remain poorly understood (Guo et al., 2017; Wang and Mandelkow, 2016).

Epileptic seizures and subclinical epileptiform activity constitute a frequent and severe comorbidity of AD, that might have an impact on cognitive status (Lam et al., 2017; reviewed in the study by Vossel et al., 2017). The incidence of seizures has also been described in patients with different types of FTLD including those with MAPT mutations (reviewed in the study by Sánchez et al., 2018). Obvious evidence speaks for a link between Tau and seizure occurrence. First, Tau hyperphosphorylation and misfolding have been observed in patients with epilepsy as well as in different related experimental models (reviewed in the study by Sánchez et al., 2018). Second, Tau reduction limits excessive network excitability in various experimental models of seizures (DeVos et al., 2013; Gheyara et al., 2014; Holth et al., 2013; Ittner et al., 2010; Roberson et al., 2007). Whether Tau pathology itself promotes the development of seizures independent of A β , and whether it correlates to memory deficits, remains unclear. Few studies have been

* Corresponding author at: Inserm UMR-S1172, "Alzheimer & Tauopathies", Place de Verdun, 59045 Lille, Cedex, France. Tel +33320298850; fax: +33320538562.

** Corresponding author at: Department of Neurosurgery, Robert Wood Johnson Medical School, Rutgers University, 683 Hoes Lane West, Piscataway, NJ 08854, USA. Tel.: +1 732 235 6373; fax: +1 732 357 6710.

E-mail addresses: detlev.boison@rutgers.edu (D. Boison), david.blum@inserm.fr (D. Blum).

Equal contributions.

performed in models of tauopathy overexpressing human Tau protein bearing FTL-D-MAPT-related mutations (García-Cabrero et al., 2013; Maeda et al., 2016; Van Erum et al., 2020). Overall, these studies demonstrate a higher susceptibility to the pro-convulsant GABA_A receptor antagonist pentylenetetrazol (PTZ) as compared to wild-type littermate mice. However, presence of spontaneous epileptiform activity and occurrence of these latter phenomena earlier or concomitantly to memory impairments remain unclear. In the present study, we evaluated the impact of Tau pathology toward spontaneous electrographic seizure occurrence and the response of seizure thresholds to PTZ using the THY-Tau22 mouse model of tauopathy, known to progressively develop hippocampal Tau pathology together with spatial memory impairments (Burnouf et al., 2013; Van der Jeugd et al., 2013).

2. Methods

Male THY-Tau22 (Tau22) and littermate wild-type (WT) mice, taken as controls [pure C57Bl/6J background], were kept in standard animal cages as described (Schindowski et al., 2006). Experiments were performed in an AAALAC-accredited facility in compliance with the principles outlined in the NIH Guide for the Care and Use of Laboratory animals and under approval by the Institutions Animal Care and Use Committee.

EEG electrodes were implanted in THY-Tau22 mice and age-matched WT littermates at 6 (n = 7/genotype) and 12 months of age (n = 4 WT and n = 9 Tau22). Briefly, each mouse was anesthetized (1.5%–2% isoflurane) and equipped with (1) a bipolar stainless steel electrode (insulated except for 80–100 μm vertically exposed at the tip; tip diameter 5-μm; vertical tip separation 200–250 μm; Plastics One Inc) unilaterally implanted into the hippocampal CA1 subregion using stereotaxic coordinates (AP = −2.1 mm; ML = −1.8 mm; DV = −1.7 mm with bregma as reference); (2) a cortical monopolar screw electrode placed over the frontal cortex; (3) and a monopolar screw ground electrode over the cerebellum. All electrodes were secured to the skull with dental cement. After recovery from surgery, all animals were continuously recorded by EEG for at least 72 hours. Electrical brain activity was monitored using a Nervus EEG recording system connected with a Nervus Magnus 32/8 Amplifier. The digital EEG signal was band-pass filtered (high-pass filter 1.0 Hz cut off, low-pass 50 Hz) and analyzed using the LabChart version 7 software (AD Instruments). EEGs were assessed for seizure activity as defined as high-amplitude rhythmic discharges that represented a new pattern of tracing (repetitive spikes, spike-and-wave discharges, or slow waves) lasting at least 5 seconds.

The seizure thresholds of 6- and 12-month-old WT and Tau22 mice were assessed with escalating doses of PTZ (n = 10/genotype/age). PTZ (Sigma P6500) was dissolved at 3.5 mg/kg in sterile 0.9% NaCl and delivered i.p. with a starting dose of 20 mg/kg, followed by additional doses of 5 mg/kg every 5 minutes. During each 5-min period, mice were evaluated for the presence of Straub's tail, clonic convulsions, hindlimb extension, and death. Data are expressed as survival curves with the percentage of nonresponding mice for each evaluation plotted relative to dose.

Western blots and histopathological evaluations and quantifications were performed in a separate group of animals as described (Gouder et al., 2004; Laurent et al., 2017; Lebouche et al., 2013). For Western blots, we used anti-GFAP (1:1000; Santa Cruz), anti-ADK (1:4000), and anti-GAPDH (1:10,000; Santa Cruz) antibodies (n = 3 genotype/age). For the histopathological evaluation, mice were transcardially perfused with 0.9% saline and 4% paraformaldehyde, brains cut into 40 μm coronal sections. Immunohistochemical detection of either GFAP (1:15,000; Chemicon International), ADK

(1:5000) or pathological Tau (AT100; 1/400) was performed as previously published (Burnouf et al., 2013; Studer et al., 2006).

Quantitative real-time PCR was performed as described (Burnouf et al., 2013). Primer sequences used are as follows: 5'-tgtagctgacatctgcaaaaa-3' (GAD65 forward), 5'-gggacatcagtaacctcca-3' (GAD65 reverse), 5'-agcatacaggctctggcatc-3' (cyclophilin A forward), 5'-ttcaccttccaaagaccac-3' (cyclophilin A reverse). Cyclophilin A was used as internal control. Amplifications were carried out in triplicate and the relative expression of target genes was determined by the $\Delta\Delta CT$ method.

For microdialysate analysis of hippocampal GABA, 12-month-old Tau22 mice (n = 6) or WT (n = 8) were anesthetized with urethane (1.62 g/kg/i.p.) and placed in a stereotaxic frame (David Kopf) with the body temperature maintained close to 37.5°C using a heated under-blanket (Harvard Instruments, USA). Homemade microdialysis probes with a 1-mm regenerated cellulose membrane (NeuroDialyTics facility, Lyon Neuroscience Research Center, France) was randomly implanted in the right or left dorsal hippocampus (AP −1.8 mm, ML ±1.5 mm, DV −2.4 mm). Probes were perfused at a rate of 1 μL/min with artificial cerebrospinal fluid (aCSF) (149 mM NaCl, 2.80 mM KCl, 1.2 mM MgCl₂, 1.2 mM CaCl₂, 2.78 mM phosphate buffer, pH 7.4). At least 2 hours elapsed before collection of basal samples (fractions 1, 2, and 3), collected every five minutes. In situ depolarization was induced for 15 minutes (fractions 4, 5, and 6) in both groups by switching the inlet of the probe with a aCSF containing a high concentration of potassium (51.8 mM NaCl, 100 mM KCl, 1.2 mM MgCl₂, 1.2 mM CaCl₂, 2.78 mM phosphate buffer, pH 7.4). Fractions 7 to 10 corresponded to perfusion with normal aCSF for washing and return to baseline. At the end of the experiment, the placement of the cannula was verified on the frozen hemisphere. Collected dialysates were stored and kept at −80°C before analyses, performed using capillary electrophoresis with laser-induced fluorescence detection (Sauvinet et al., 2003).

Data were analyzed using GraphPad Prism software (GraphPad Software, La Jolla, CA, USA) using Student's *t*, two-way ANOVA followed by Bonferroni post-hoc analysis and Mantel-Cox (Log-rank) test for the survival curves. The null hypothesis was rejected at the *p* = 0.05 level for all analyses.

3. Results

We first determined if Tau pathology is sufficient to elicit spontaneous seizures. In the THY-Tau22 strain, hippocampal pathology substantially progresses from 6 to 12 months of age (Schindowski et al., 2006). Importantly, at the age of 6 months, THY-Tau22 mice do not exhibit spatial memory impairments while at 12 months, these mice show significant alterations (Burnouf et al., 2013; Carvalho et al., 2019; Van der Jeugd et al., 2013). EEG recordings obtained from hippocampal depth electrodes implanted into the CA1 of 6- and 12-month-old mice were found to be similar to the brain activity of WT littermates (Fig. 1). Cumulative recording times of at least 500 hours did not reveal a single electrographic seizure. EEGs were without changes in the spike waveform that are indicative of spontaneous electrographic seizures or epileptiform activity (Fig. 1A and F). Despite a lack of spontaneous electrographic seizures in the mutant mice, Tau pathology led to a moderate increase in seizure susceptibility (Fig. 1B–D). Using the PTZ seizure threshold test, overall, THY-Tau22 mice progressed from Straub's tail (Fig. 1B and G), to clonus extension (Fig. 1C and H) and finally hindlimb extension (Fig. 1D and I) at a lower dose of PTZ than WT littermates. There was also a trend toward increased mortality in the Tau22 mice (Fig. 1E and I). Therefore, Tau pathology increases seizure susceptibility, although insufficient to cause epileptic seizures by itself. Several mechanisms may be involved in the

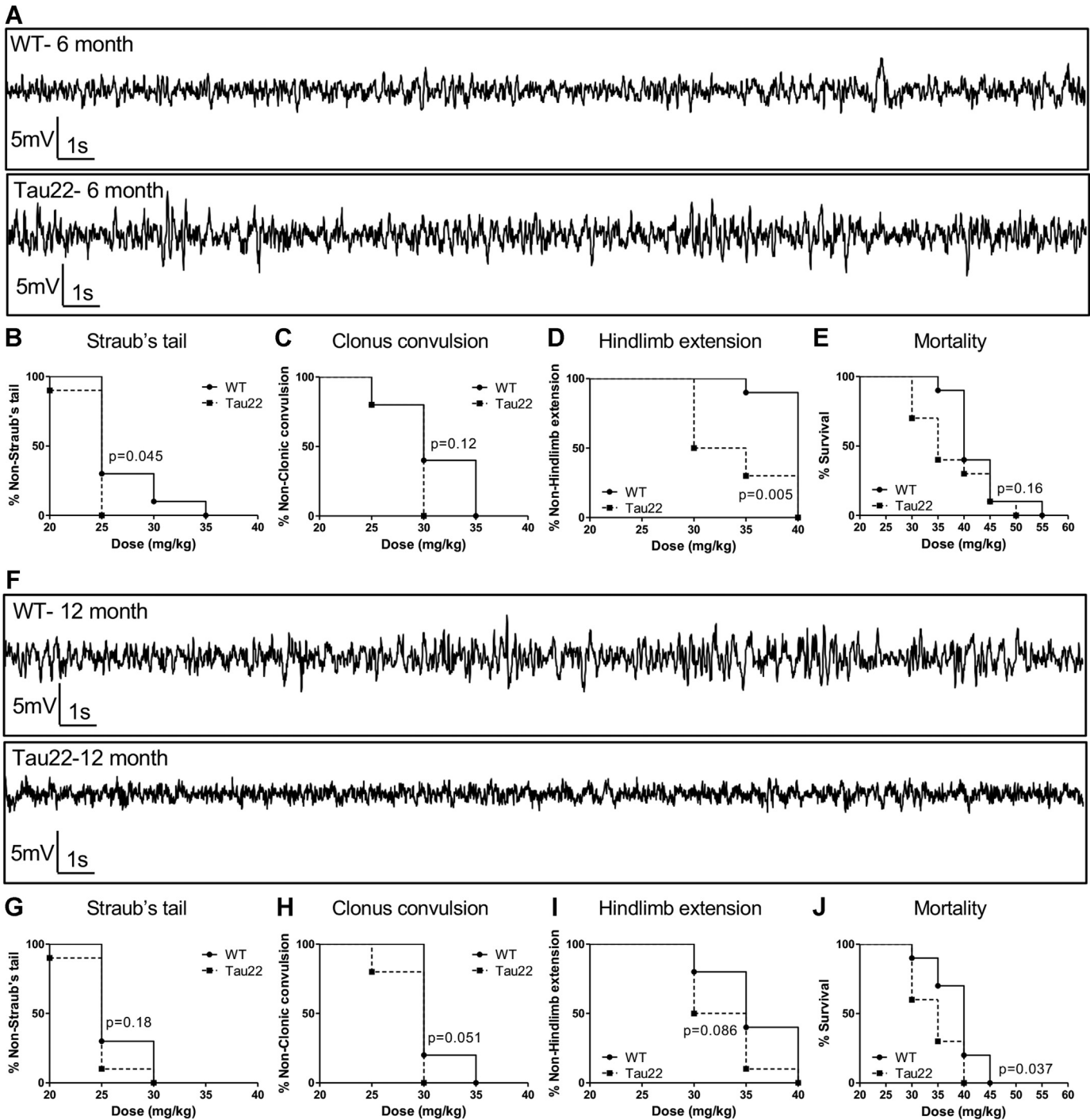


Fig. 1. Tau pathology decreases seizure threshold but is not sufficient to cause spontaneous electrographic seizures. (A) Representative hippocampal electroencephalographic (EEG) traces from a 6-month-old mutant Tau22 mouse and wild-type (WT) littermate are both indicative of normal brain activity. (B–D) The Straub's tail (B); clonus extension (C); and hindlimb extension (D) responses of 6-month-old WT and Tau22 mice to escalating pentylenetetrazol (PTZ) doses. The percent of Tau22 mice that elicit Straub's tail (B) and hindlimb extension (D) at a lower PTZ dose is significantly different from the response in WT mice. (E) Percent mortality in response to PTZ dose is equivalent between 6-month-old Tau22 and control mice. (F) Representative hippocampal EEG traces from a 12-month-old Tau22 mutant and WT control are both indicative of normal brain activity. (G–I) The Straub's tail (G); clonus extension (H); and hindlimb extension (I) responses of 12-month-old WT and Tau22 mice to escalating PTZ doses. (J) The percent mortality in response to increasing doses of PTZ is significantly increased in 12-month-old Tau22 mice, compared to controls. PTZ threshold data are plotted as percent survival curves ($n = 10/\text{genotype}$) and analyzed with a Mantel-Cox (log-rank) test.

increased seizure susceptibility to PTZ. Here, we sought to investigate if Tau pathology modulates the expression of markers typically associated with network hyperexcitability and seizures such as astrocytic and GABA-related markers. First, we identified a significant hippocampal increase of the astroglial marker GFAP at both 6

and 12 months of age in Tau mice (Fig. 2A–C). This coincided with a delayed increase in adenosine kinase (ADK) expression in transgenic animals (Fig. 2D–F). Noteworthy, Tau pathology, as marked by the conformational AT100 antibody, is significantly enhanced between these 2 time points (Fig. 2G–I). In addition, while we found a

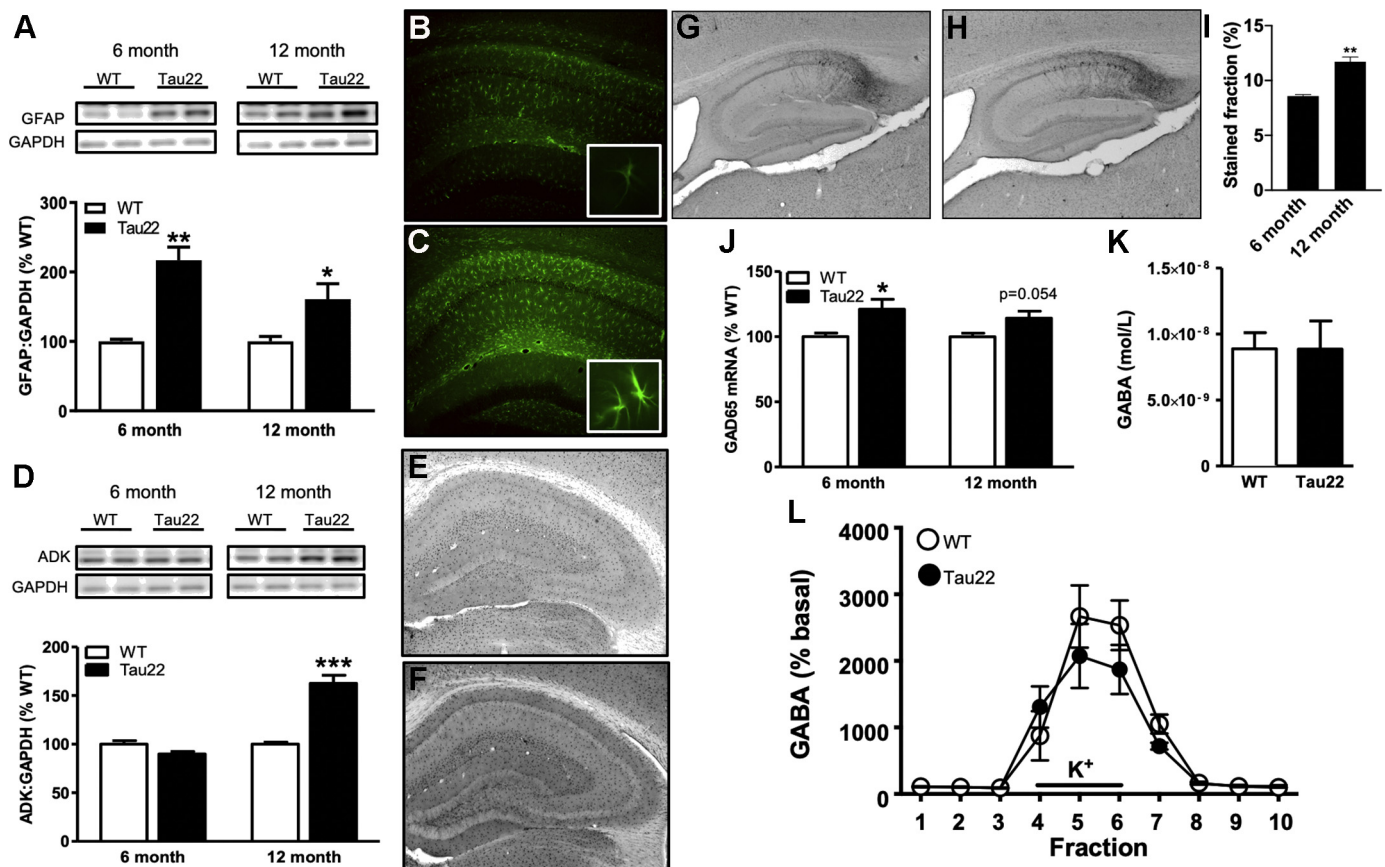


Fig. 2. Tau pathology is associated with increased astrogliosis and expression of ADK and GAD65. The astrogliosis markers GFAP and ADK are increased in the hippocampus of Tau22 mutants compared to age-matched controls. (A) Upper panel: representative GFAP and GAPDH Western blots. Lower panel: densitometry analysis of the GFAP/GAPDH ratio identifies a significant increase in hippocampal GFAP protein levels in the 6- and 12-month-old Tau22 mutants (black bars), compared to age-matched WT littermates (white bars). GFAP measurements are normalized to GAPDH and expressed as percent of control (mean \pm SEM, $n = 3$ per age and genotype). (B and C) Representative images of GFAP immunohistochemistry in the hippocampal formation of 12-month-old WT (B) and Tau22 (C) mice. Insets are higher magnification images of astrocytes obtained from the respective fields in panels B and C. (D) Upper panel: representative ADK and GAPDH Western blots. Lower panel: densitometry analysis of the ADK/GAPDH Western blot indicates a significant increase in hippocampal ADK protein levels at 12 months of age in the Tau22 mutants (black bars), compared to controls (white bars). ADK measurements are normalized to GAPDH and expressed as percent of control (mean \pm SEM, $n = 3$ per age and genotype). (E and F) Representative images of ADK immunohistochemistry in the hippocampal formation of 12-month-old WT (E) and Tau22 (F) mice. (G–I) Representative images of AT100 tau immunohistochemistry in the hippocampal formation of 6- (G) and 12-month-old (H) Tau22 mice and related quantification (I). (J) Quantitative PCR for GAD65 mRNA indicates a significant genotype effect ($p = 0.0045$) with a significant increase at 6 months of age and a trend toward increased expression at 12 months of age within the Tau22 hippocampus, compared to the age-matched controls. Data are normalized to cyclophilin A and expressed as percent of control (mean \pm SEM, $n = 5$ Tau22 and $n = 6$ WT per age). (K and L) GABA concentrations in microdialysates obtained in the dorsal hippocampus of anesthetized 12-month-old Tau22 ($n = 6$, in black) and WT mice ($n = 8$, in white) are equivalent. (K) The basal levels represented as histograms were calculated as the mean \pm SEM of the 3 consecutive 5-minute microdialysates following the 2-h equilibration period and preceding K^+ depolarization. (L) The effect of a 15-minute potassium-induced depolarization (black line) on GABA extracellular concentrations (circles) monitored at a 5-minute sampling rate. Data are expressed as percent (mean \pm SEM) of the 3 baseline values preceding K^+ depolarization. No statistical difference was revealed. All data were analyzed by two-way ANOVA followed by Bonferroni post hoc analysis when appropriate (* < 0.05 ; ** < 0.01 , *** < 0.0001).

moderate increase in GAD65 expression in THY-Tau22 as compared to WT (Fig. 2J), basal GABA levels revealed no statistical difference between WT and Tau22 mice (Fig. 2K). Furthermore, responses to potassium-induced depolarization were also examined; and in spite of a downward trend, the release of GABA induced by 100 mmol/L K^+ for Tau 22 mice was not statistically different from that in WT mice (Fig. 2L).

4. Discussion

Accumulation of A β into plaques and Tau in neurofibrillary degeneration are the 2 hallmarks of AD. While the role of A β into the development of AD-related seizures has been well investigated (reviewed in the study by Vossel et al., 2017), the involvement of Tau pathology, and relationship to memory impairments remained ill-defined. Here, we used the progressive THY-Tau22 strain to investigate the link between Tau pathology development,

hippocampal memory deficits and seizure occurrence, as well as susceptibility to PTZ. Evaluations were performed at 6 months of age, when pathology is present, but memory unaffected, and 12 months of age when hippocampal pathology and memory impairments culminate (Van der Jeugd et al., 2013). Moreover, during this period, neuroinflammation, a known contributor to the pathophysiology of epilepsy (Vezzani et al., 2019), is ongoing and participate to memory deficits (Ising et al., 2019; Laurent et al., 2016, 2017).

Our results suggest that established Tau pathology unlikely leads to spontaneous seizure occurrence. However, the PTZ data indicate that Tau pathology reduced seizure threshold as early as 6 months, when hippocampal-dependent memory is not impaired. It seems unlikely that susceptibility to PTZ relates to Tau pathology itself. Indeed, while the latter is substantially enhanced between 6 and 12 months of age in the THY-Tau22 strain, this does not lead to a particular enhancement of susceptibility to PTZ. Excitability

changes might therefore relate to either soluble toxic species and/or Tau overexpression as previously suggested in another transgenic Tau model (Maeda et al., 2016). Several mechanisms could be involved in the observed increased seizures susceptibility (reviewed in the study by Vossel et al., 2017), such as glutamate spillover that may occur through impaired glial transporters and/or impaired presynaptic release, alterations of GABA or GABAergic interneurons, or metabolism of the endogenous anticonvulsant adenosine through astrocytic ADK. In a former study, we demonstrated that THY-Tau22 mice exhibit increased hippocampal levels of glutamate (Laurent et al., 2016) and an increase in the glutamatergic drive in CA1 (Zappettini et al., 2019), which might be implicated in the increased susceptibility to PTZ found in Tau mice. Conversely, while Tau mice exhibit a slight change in GAD mRNA expression, steady-state and induced GABA levels were not found altered in Tau mice, presumably excluding an involvement in the PTZ phenotype.

Interestingly, we found that PTZ sensitivity was associated with a significant increase in astroglial ADK levels at 12 months of age. Increased levels of ADK are a pathological hallmark of both epilepsy and AD (Aronica et al., 2013). It has also been documented that increased levels of ADK can be a direct cause for the generation of spontaneous electrographic seizures (Li et al., 2008). The lack of spontaneous electrographic seizures in the THY-Tau22 mice was therefore an unexpected finding. However, we found a reduction of PTZ seizure thresholds, which is in line with increased ADK expression and a concomitant reduction of the inhibitory adenosinergic tone.

Overall, our results show that THY-Tau22 pathology is not sufficient to generate spontaneous subclinical seizures, but our results clearly show that the THY-Tau22 pathology can reduce seizure thresholds independently of A β . In contrast to Tau models, previous data from transgenic amyloidogenesis models clearly demonstrate the occurrence of spontaneous seizures (Minkeviciene et al., 2009; Palop et al., 2007). Reasons for such discrepancy remain unclear, but it may potentially depend on the enhanced ability of amyloid peptides and plaques to promote microglia and astrocytic neuroinflammation (Sierksma et al., 2020) known to strongly contribute to seizure development (Vezzani et al., 2011), as well as to memory impairments (Ising et al., 2019; Laurent et al., 2017). Further, amyloid- β induced seizures depend on the presence of tau (Roberson et al., 2007), suggesting that the development of Tau pathology may further aggravate A β -driven seizures in AD.

Disclosure statement

The authors declare no conflict of interest.

CRediT authorship contribution statement

Victoria Gomez-Murcia: Methodology, Formal analysis, Writing - original draft, Writing - review & editing. **Ursula Sandau:** Methodology, Formal analysis, Writing - original draft, Writing - review & editing. **Barbara Ferry:** Methodology, Formal analysis, Writing - original draft, Writing - review & editing. **Sandrine Parrot:** Methodology, Formal analysis, Writing - original draft, Writing - review & editing. **Cyril Laurent:** Methodology, Formal analysis, Writing - original draft, Writing - review & editing. **Marie Basquin:** Methodology, Formal analysis, Writing - review & editing. **Detlev Boison:** Conceptualization, Formal analysis, Writing - original draft, Writing - review & editing. **David Blum:** Conceptualization, Formal analysis, Writing - original draft, Writing - review & editing.

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