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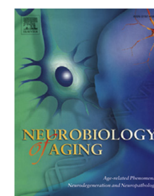

Hippocampal neurophysiology is modified by a disease-associated C-terminal fragment of tau protein

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ABSTRACT

The accumulation of cleaved tau fragments in the brain is associated with several tauopathies. For this reason, we recently developed a transgenic mouse that selectively accumulates a C-Terminal 35 kDa human tau fragment (Tau35). These animals develop progressive motor and spatial memory impairment, paralleled by increased hippocampal glycogen synthase kinase 3β activity. In this neurophysiological study, we focused on the CA1 subfield of the hippocampus, a brain area involved in memory encoding. The accumulation of Tau35 results in a significant increase of short-term facilitation of the synaptic response in the theta frequency range (10 Hz), without affecting basal synaptic transmission and long-term synaptic plasticity. Tau35 expression also alters the intrinsic excitability of CA1 pyramidal neurons. Thus, Tau35 presence is associated with increased and decreased excitability at hyperpolarized and depolarized potentials, respectively. These observations are paralleled by a hyperpolarization of the voltage-sensitivity of noninactivating K^+ currents. Further investigation is needed to assess the causal link between such functional alterations and the cognitive and motor impairments previously observed in this model.

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1. Introduction

A range of neurodegenerative tauopathies in humans are characterized by the progressive accumulation of pathogenic tau aggregates within the central nervous system (CNS). These conditions are associated with diverse clinical outcomes, which may consist of both cognitive and motor impairments, as extensively reviewed (Goedert and Spillantini, 2011; Lee et al., 2001; Spillantini and Goedert, 2013). Alzheimer's disease represents the most common form of tauopathy. Its pathological outcomes coexist with, and may be a consequence of, amyloidopathy (Hardy and Allsop, 1991; Hardy and Higgins, 1992). Neurodegenerative diseases that are purely associated with the progressive accumulation of tau protein species, include frontotemporal dementia (FTD), progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD). PSP is characterized histopathologically by neurodegeneration of midbrain and brainstem structures, including hypothalamus and basal ganglia (Pollock et al., 1986) and clinically by postural instability (Steele et al., 1964).

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In tauopathy, the tau protein can be subjected to a range of disease-associated posttranslational modifications, the most explored one being its phosphorylation. The altered phosphorylation of tau protein leads to the formation of neurofibrillary tangles, and the occlusion of its ability to interact with microtubules; hyperphosphorylated tau is associated with all the previously mentioned neurodegenerative conditions (Spillantini and Goedert, 2013). Ubiquitination and tau truncation are also characteristic modifications observed in human tauopathies (Martin et al., 2011).

The majority of tauopathies are sporadic, and some lines of evidence suggest that the accumulation of tau fragments plays a part in the pathogenesis of some or all of these conditions. For instance, we previously identified a N-terminally truncated form of tau in human brain that is highly phosphorylated and associated with the development of 4-repeat forms of human tauopathy, such as PSP (Guo et al., 2017; Wray et al., 2008). This work on human disease tissues was followed-up by the production of a novel mouse model in which the brain-derived, C-terminal 35 kDa tau fragment (Tau35) was expressed under the control of the human tau promoter (Bondulich et al., 2016). The expression of the construct was introduced into the mouse hypoxanthine phosphoribosyl transferase (*Hprt*) locus (Bronson et al., 1996), guaranteeing single copy targeted integration. This both eliminates potential gene disruption

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around the insertion site and avoids artifacts due to tau overexpression. Correspondingly, in this animal, the Tau35 transgene was only expressed at a low level, accounting for less than 10% of the level of endogenous mouse tau.

Tau35 mice progressively develop a number of key aspects of human tauopathies. These include the appearance of aggregated and abnormally phosphorylated tau, increased glycogen synthase kinase 3β (GSK3β) activity, deficits in cognitive and motor function, premature death, dysfunction associated with autophagy and lysosomal processing, and a decline in synaptic protein levels. Cognitive decline was revealed in Tau35 mice by an age-dependent impairment in their performance in the Morris water maze, a well-validated hippocampal-dependent spatial memory task (Bondulich et al., 2016).

This work examines the neurophysiological function of the Tau35 mouse in the CA1 subfield of the hippocampus, an area with a well-established role in spatial navigation and memory (Chersi and Burgess, 2015). The experiments were all performed on mice aged 14–18 months. This is an age beyond which water maze learning is eliminated and is the age point at which biochemical and immunohistochemical measurements revealed a number of key alterations to hippocampal neurochemistry. These include tangle-like structures reactive for a broad range of tau antibodies, changes to tau phosphorylation, increased GSK-3β activity, altered levels of synaptic proteins, and modifications indicative of altered autophagic processing (Bondulich et al., 2016). Our experiments reveal that, as seen in other models of tauopathy (Booth et al., 2016b), long-term synaptic plasticity is unaltered in the Schaffer collateral commissural pathway. However, we did observe genotype-associated changes to short-term synaptic plasticity and intrinsic excitability properties of CA1 pyramidal neurons that may contribute to the loss of spatial memory these mice exhibit.

2. Materials and methods

2.1. Experimental animals

In all experiments, animals expressing the Tau35 transgene were compared against age-matched wild-type littermate controls (36 animals; 17 WT, 19 TG). Fig. 1 shows a schematic representation of the Tau35 fragment compared to human tau; this is the product of the expression of the Tau35 genetic construct described in our previous work (Bondulich et al., 2016). Animals were bred at King's College London and arrived in a single shipment to the University of Exeter Medical School prior to the commencement of the study. They were group housed, allowed food and water ad libitum and maintained on a 12:12 hours light/dark cycle. This study was carried out in accordance with UK Home Office Guidelines and the King's College London and University of Exeter Animal Welfare Ethical Review Board.

2.2. Preparation of brain slices

Animals were sacrificed using cervical dislocation in accordance with Schedule 1 of the Animals (Scientific Procedures) Act (1986). The brain was rapidly removed and transferred to an ice cold cutting solution consisting of (in mM): 189 sucrose, 10 D-glucose, 26 $NaHCO_3$, 3 KCl, 5 $MgSO_4(7H_2O)$, 0.1 $CaCl_2$, and 1.25 NaH_2PO_4. About 300-μm coronal sections were cut using a Leica VT1200 microtome and immediately transferred to a holding chamber containing artificial cerebrospinal fluid (aCSF) continuously bubbled with carbogen. The composition of the aCSF was as follows (in mM): 124 NaCl, 3 KCl, 24 $NaHCO_3$, 2 $CaCl_2$, 1.25 NaH_2PO_4, 1 $MgSO_4$, and 10 D-glucose. The slices were then allowed to recover for 30 minutes at 37 °C and subsequently at room temperature for at least 1 hour before transfer into a recording chamber. Field potential and whole-cell recording experiments were carried out on different brain slices.

2.3. Whole-cell patch-clamp recordings

Slices were transferred to a recording chamber where they were submerged in carbogen-equilibrated aCSF and maintained at a temperature between 33 °C–34 °C. The recording chamber was secured on the stage of an Olympus BX51 upright microscope and individual CA1 pyramidal neurons were visualized using infrared differential interference contrast optics. Borosilicate glass microelectrodes with a resistance ranging from 3–5 MΩ were pulled, fire-polished, and filled with a K-gluconate–based internal solution consisting of (in mM): 135 K-gluconate, 5 NaCl, 10 HEPES free acid, 0.2 EGTA, 0.3 Na-GTP, 4 Mg-ATP, and 13.4 Biocytin (pH 7.3, 280–290 mOsm). Following entry into whole-cell configuration, a junction potential error of 15 mV arose due to the pairing of the pipette solution with the aCSF, which was arithmetically corrected for during analysis. Signals were recorded using a Multiclamp 700B amplifier, digitized using a Digidata 1440, and stored for future analysis using pClamp 10 software.

All recordings were made from a defined prestimulus membrane potential set by injecting a continuous flow of bias current through the recording electrode. This facilitated the analysis of passive neuronal properties and action potential (AP) generation from prestimulus membrane potentials (V_m) of both −80 and −74 mV. To measure neuronal passive membrane properties, a 500 ms, −100 pA hyperpolarizing current step was injected across the membrane from each V_m. The subsequent voltage deflection at the steady state of the hyperpolarization was used to calculate the input resistance (R_{in}) of the membrane using Ohm's law ($V = IR$). The extrapolation of a single exponential curve at an infinite time, fitted to the membrane charging response between 10% and 95% of the peak amplitude, was used to calculate the membrane time constant (τ). An approximation of capacitance was measured as the ratio between the τ and R_{in}. Sag, measured as the difference between the negative peak and the steady state hyperpolarization, was expressed as a percentage of the peak hyperpolarization in response to a 500 ms, −100 pA hyperpolarizing current injection.

Standard "Zap" protocols were used to measure subthreshold membrane resonance properties, as previously described (Hu et al., 2002; Tamagnini et al., 2014). Briefly, the ratio of the fast Fourier transform of the voltage response versus the current injection was calculated as a measure of the impedance profile of the pyramidal neurons ($Z = V_{fft}/I_{fft}$). Subsequently, the impedance versus

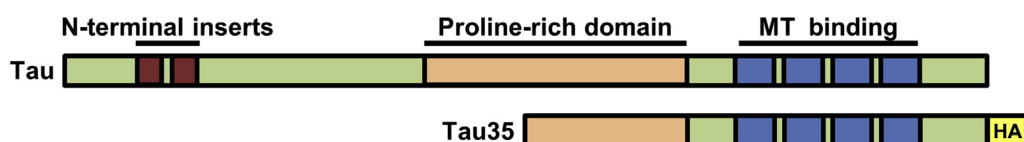

Fig. 1. Schematic representation of the Tau35 fragment in comparison to full-length human tau. Tau is alternatively spliced, and the largest CNS isoform of human tau comprises 2 N-terminal inserts, followed by a proline-rich domain and 4 microtubule binding repeats (2N4R tau, 441 amino acids). The Tau35 sequence includes residues 187-441 of 2N4R human tau fused at the C-terminus to a hemagglutinin tag (HA). Abbreviations: CNS, central nervous system; Tau35, C-Terminal 35 kDa human tau fragment.

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