Neurobiology of Disease 127 (2019) 582–590

Contents lists available at ScienceDirect

Neurobiology of Disease

journal homepage: www.elsevier.com/locate/ynbdi

Soluble tau aggregates inhibit synaptic long-term depression and amyloid β-facilitated LTD *in vivo*

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ARTICLE INFO

Keywords:
Alzheimer's disease
Microtubule-associated protein tau
Amyloid β-protein
Synaptic plasticity
Rat hippocampus

ABSTRACT

Soluble synaptotoxic aggregates of the main pathological proteins of Alzheimer's disease, amyloid β-protein (Aß) and tau, have rapid and potent inhibitory effects on long-term potentiation (LTP). Although the promotion of synaptic weakening mechanisms, including long-term depression (LTD), is posited to mediate LTP inhibition by Aß, little is known regarding the action of exogenous tau on LTD. The present study examined the ability of different assemblies of full-length human tau to affect LTD in the dorsal hippocampus of the anaesthetized rat. Unlike Aß, intracerebroventricular injection of soluble aggregates of tau (SτAs), but not monomers or fibrils, potently increased the threshold for LTD induction in a manner that required cellular prion protein. However, MTEP, an antagonist of the putative prion protein coreceptor metabotropic glutamate receptor 5, did not prevent the disruption of synaptic plasticity by SτAs. In contrast, systemic treatment with Ro 25–6981, a selective antagonist at GluN2B subunit-containing NMDA receptors, reduced SτA-mediated inhibition of LTD, but not LTP. Intriguingly, SτAs completely blocked Aß-facilitated LTD, whereas a subthreshold dose of SτAs facilitated Aß-mediated inhibition of LTP. Overall, these findings support the importance of cellular prion protein in mediating a range of, sometimes opposing, actions of soluble Aß and tau aggregates with different effector mechanisms on synaptic plasticity.

1. Introduction

Early loss of synapses preceding neuronal death is a hallmark of Alzheimer's disease (AD) (West et al., 1994). In humans, synapse loss highly correlates with cognitive impairment, more than the presence of amyloid plaques or neurofibrillary tangles (Terry et al., 1991). Preclinical AD is, therefore, likely to be characterized by synaptic dysfunction. Long-term potentiation (LTP), which involves the activity-dependent persistent strengthening of synaptic transmission, is especially sensitive to the disruptive actions of the two key pathological proteins, Aß and tau (Cullen et al., 1997; Lasagna-Reeves et al., 2011). In particular, certain soluble aggregated forms of these proteins appear to be the most synaptotoxic species (Medina and Avila, 2014; Selkoe and Hardy, 2016). Indeed, Aß oligomers (Aßo) rapidly and potently inhibit LTP at least partly *via* a cascade of events that is initiated by the binding of Aßo to another key protein, cellular prion protein (PrP^C) (Lauren et al., 2009; Purro et al., 2018). Very recently, we discovered the inhibition of LTP by application of exogenous soluble aggregates of tau (SτAs) *in vivo* is also PrP-dependent (Ondrejcak et al., 2018), consistent with the hypothesis that PrP^C is a common receptor site for synaptotoxic Aß and tau (Resenberger et al., 2011).

Apart from inhibiting LTP in a PrP-dependent manner, Aßo exert the opposite effect on 'synaptic weakening' pathways by enhancing long-term depression (LTD) (Kim et al., 2001), also *via* PrP^C (Hu et al.,

Abbreviations: AD, Alzheimer's disease; Aß, amyloid beta; Aßo, Aß oligomers; EPSPs, excitatory postsynaptic potentials; HFS, high frequency stimulation; i.c.v., intracerebroventricularly; i.p., intraperitoneally; LFS, low frequency stimulation; LTD, long-term depression; LTP, long-term potentiation; n.s., not significant; mGlu5R, metabotropic glutamate receptor subtype 5; NMDAR, NMDA receptor; PrP^c, cellular prion protein; SτAs, soluble aggregates of tau

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https://doi.org/10.1016/j.nbd.2019.03.022
Received 19 December 2018; Received in revised form 1 March 2019; Accepted 21 March 2019
Available online 22 March 2019
0969-9961/

2014). Assuming similar mechanisms underlie the requirement for PrP^C in SτA- and Aß-mediated inhibition of LTP, the question arises as to whether or not SτAs also can facilitate LTD in a PrP-dependent manner. Such facilitation would support and extend proposals that promotion of 'synaptic weakening' pathways may mediate disruption of synaptic plasticity and eventual synaptic loss in early AD pathogenesis (Collingridge et al., 2010; Hu et al., 2014; Kessels and Malinow, 2009; Ondrejcak et al., 2010; Whitehead et al., 2017).

To our surprise, we found that SτAs cause a rapid and PrP-dependent inhibition of LTD in the rat hippocampus *in vivo* and that SτAs also blocked Aßo-facilitated LTD. These findings do not support a general 'synaptic weakening' hypothesis for the disruptive actions of SτAs. Rather, the data strongly indicate that SτAs reduced the dynamic range of synaptic plasticity and that PrP^c can act as a common mediator of soluble Aß and tau-mediated synaptotoxicity, albeit with opposite effects on LTD.

2. Materials and methods

2.1. Animals and surgery

Animal care and experimental protocols were carried out in accordance with the approval of the Health Products Regulatory Authority, Ireland. Adult (180–350 g, 7–11 weeks old) male Lister hooded rats, supplied by the Comparative Medicine Unit, Trinity College Dublin, were housed under a 12-h light-dark cycle at room temperature (19–22 °C). Animals were anaesthetized with urethane (1.5–1.6 g/kg, i.p.), and a stainless-steel cannula (22 gauge, 0.7 mm outer diameter, length 13 mm) was implanted above the right lateral ventricle (1 mm lateral to the midline and 4 mm below the surface of the dura). Intracerebroventricular (i.c.v.) injections were made *via* an internal cannula (28 gauge, 0.36 mm outer diameter) using a Hamilton syringe. Verification of the placement of cannula was performed post-mortem by checking the spread of ink dye.

2.2. Stimulation and recording in vivo

Teflon-coated tungsten wire monopolar recording electrodes and twisted bipolar stimulating electrodes were implanted in the CA1 area of the right dorsal hippocampus using stereotaxic coordinates relative to bregma. The recording wire was located 3.4 mm posterior to bregma and 2.5 mm lateral to midline, and stimulating wire 4.2 mm posterior to bregma and 3.8 mm lateral to midline. Electrode placement was optimized using electrophysiological criteria and confirmed post-mortem.

Field excitatory postsynaptic potentials (EPSPs) were evoked and recorded in the stratum radiatum. Single square-wave pulse (0.2 ms duration) was applied at 0.033 Hz and an intensity that triggered a 50% maximum EPSP response. To induce LTD a 1 Hz low-frequency stimulation (LFS) protocol consisting of 300, 600 or 900 pulses (0.2 ms duration) with the intensity raised to trigger EPSPs of 95% maximum amplitude was applied. To induce LTP a 200 Hz high-frequency stimulation (HFS) protocol consisting of one set of 10 trains of 20 pulses (inter-train interval of 2 s) at test intensity was applied. There were no detectible abnormal changes in background hippocampal EEG which was monitored throughout the experiments. Control experiments were interleaved throughout.

2.3. Recombinant tau preparations

As described previously (Ondrejcak et al., 2018), we investigated the effects of two different preparations of recombinant, full-length human tau (tau441, 2N4RT): wild-type (WT) and P301S tau, a more aggregation-prone sequence that is responsible for certain forms of familial dementia (Mellone et al., 2013; Sanchez et al., 2018; Spillantini and Goedert, 2013).

Wild-type tau was expressed and purified in phosphate buffered saline (PBS) as described previously (Barghorn et al., 2005; O'Dowd et al., 2013; Ondrejcak et al., 2018). Protein purity and identity were assessed by SDS-PAGE/Coomassie blue staining and mass spectrometry. Briefly, tau monomer was concentrated and 1,4-dithiothreitol was used to reduce cysteine-mediated tau dimerization. Heparin was then added to promote aggregation for 6 days at 37 °C and fibrils harvested by ultracentrifugation. Tau fibrils were ultrasonicated for 10 5 s bursts to prepare SτAs.

P301S tau (P301S_103his-tag_avi-tag full length tau441) was also expressed and purified as previously described (Ondrejcak et al., 2018). As with wild-type tau, P301S tau was aggregated by incubation with heparin. Fibrils were pelleted by ultracentrifugation, resuspended in PBS and sonicated at 100 W for 3 × 20 s to produce SτAs.

Aggregated forms of tau were quantified (based on monomer equivalent) after dispersion in guanidinium hydrochloride (GuHCl; final concentration of 2.5 M) overnight at 4 °C. Absorbance at 280 nm was measured and the concentration of tau monomer determined using the extinction coefficient $\varepsilon_{280} = 7450\ M^{-1}\ cm^{-1}$. All samples were measured in triplicate.

As described previously (Ondrejcak et al., 2018), monomers, end-stage fibrils and SτAs were characterized by EM (Supplemental Fig. 1A). Monomeric P301S and WT tau contained no structures detectable by EM, whereas end-stage aggregates contained a mixture of straight and twisted filaments. EM of SτAs revealed a mixture of species, including imperfect spheres and abundant short fibrils of approximately 4–10 nm diameter and 16–80 nm in length.

We chose the doses of tau based on pilot experiments and our previous findings on the inhibition of LTP in the absence of significant change of baseline synaptic transmission (Ondrejcak et al., 2018). In majority of experiments we only tested P301S tau. Because of the similarities in the findings, in some specified experiments we combined the results obtained with wild type and P301S tau preparations.

2.4. Soluble synthetic Aß

Aß preparations enriched with oligomers and protofibrils (Aß-derived diffusible ligands, ADDL) were prepared using synthetic Aß1–42 (synthesized by Dr. James I. Elliott at the ERI Amyloid laboratory, Oxford, CT, USA) as described previously (Hu et al., 2014; Nicoll et al., 2013). As described previously (Nicoll et al., 2013), the protofibrils are largely 10–100 nm in length with molecular weights of 105–107 and hydrodynamic radii of 8–50 nm. Briefly, the peptide was dissolved in ice-cold HFIP to a concentration of 1 mM, sonicated for 10 min and left to stand at room temperature for 1 h. The HFIP was evaporated using a stream of dry air/N_2 to produce a clear, homogenous peptide film. This film was dissolved in anhydrous DMSO to produce a 5 mM solution and then diluted to 100 μM in phenol red-free Ham's F12 medium without L-glutamine and vortexed for 15 s. The sample was centrifuged at 16,000*g* for 5 min to pellet large fibrils, and the concentration of oligomeric Aß in the supernatant was determined using size exclusion chromatography. Aliquots of ADDL were snap frozen in liquid N_2, stored at −80 °C and thawed once before use.

2.5. Drugs and antibodies

MTEP (3-((2-methyl-1,3-thiazol-4-yl)ethynyl)pyridine hydrochloride) (Abcam) was dissolved in water. Previously we reported that MTEP completely blocked Aß-facilitated LTD (Hu et al., 2014) at a dose (3 mg/kg i.p.) that has been found to achieve > 90% receptor occupancy in the brain when administered to awake rats (Busse et al., 2004).

Ro 25-6981 ([R-(R,S)]-α-(4-Hydroxyphenyl)-β-methyl-4-(phenylmethyl)-1-piperidinepropanol hydrochloride hydrate) (Sigma) was dissolved in DMSO and diluted in saline (1 ml 5% v/v). A dose of 10 mg/kg has been reported to achieve a brain concentration of 3.2 μM 1.5 h after i.p. injection (Peeters et al., 2007). Consistent with our previous report that 6 mg/kg i.p. did not affect control LTP (Hu et al.,

2009) in ongoing studies we found similar results with a dose of 12 mg/kg i.p. ($n = 5$). Moreover, this dose did not prevent LFS900-induced LTD (O'Riordan et al., 2018) but abrogated Aß-mediated inhibition of LTP (Hu et al., 2009).

The monoclonal antibody (mAb) MI-0131 (human IgG1, raised against residues 23–51 of PrP) was generated by AstraZeneca/MedImmune. 6E10 (mouse IgG1, anti-Aß N-terminus) (Biolegend, UK) was used as the control for MI-0131. 6D11 (mouse IgG2a, anti-PrP 95–105) and mouse IgG2a isotype control mAbs were also from Biolegend. The dose of mAbs initially chosen was based on our previously published finding that 20 µg (i.c.v.) of either MI-0131 or 6D11 completely prevented LTP inhibition by SτAs (Ondrejcak et al., 2018). However, because we found in pilot studies that this dose of 6D11 did not prevent the tau (SτAs, 0.6 pmol)-mediated inhibition of LTD (n = 5), we increased its dose to 40 µg.

2.6. Statistical analysis

EPSP amplitude is presented as the mean ± SEM % pre-injection baseline recorded over a 45 min period. In the time-course graphs EPSP values are presented in 5-min epochs (average of 10 sweeps). For statistical purposes the EPSP amplitude was averaged over the last 10 min epoch prior to and 170–180 min (3 h) after application of the conditioning stimulation. The ability to induce LTD/LTP within each experimental group was assessed *a priori* using paired *t*-tests. In some specified cases the interleaved vehicle-injection control experiments overlapped between experimental sets. Differences in the magnitude of LTD/LTP between experimental groups were analyzed using analysis of variance (one-way or repeated measures two-way ANOVA) with Bonferroni *post hoc* test. A P value of < 0.05 was considered statistically significant. Statistical analyses were performed with Prism 6.0.

3. Results

3.1. Soluble tau aggregates impair LTD in vivo

Because tau aggregates prepared by sonicating fibrils potently inhibit LTP (Ondrejcak et al., 2018) in a manner similar to Aßo (Yang et al., 2017), we predicted that such soluble tau aggregates (SτAs) would, as with Aßo, enhance LTD. Hence, we first tested the effects of intracerebroventricular (i.c.v.) injection of SτAs on the ability of a relatively weak, low frequency conditioning stimulation protocol, 300 high-intensity pulses at 1 Hz (LFS300), to induce LTD. Contrary to our hypothesis, small but significant LTD triggered by the application of LFS300 in the vehicle group (Veh, 80.6 ± 2.9% at 3 h post LFS, $n = 6$, $P = .004$ compared with 10 min epoch pre LFS300; paired t) was completely inhibited after acute injection (0.6 pmol, i.c.v.) of SτAs (100.9 ± 3.2%, $n = 5$, $P = .5153$ compared with pre, paired t; $P < .0001$ compared with vehicle, RM-2W-ANOVA, followed by Bonferroni post-hoc test) (Fig. 1A, B).

We wondered if SτAs inhibited LTD by increasing the induction threshold. Therefore, we increased the strength of the induction protocol by increasing the number of pulses to either 600 (LFS600) or 900 (LFS900). The same dose (0.6 pmol, i.c.v.) of SτAs that inhibited LFS300-induced LTD also inhibited that induced by LFS600 (Fig. 1C, D). Thus, the EPSP at 3 h post-LFS600 decreased significantly in the vehicle-treated group (Veh, 64.3 ± 5.8%, $n = 5$, $P = .0032$ compared with pre, paired t) but not in the group injected with 0.6 pmol SτAs 15 min prior to LFS600 (SτAs pre, 99.6 ± 2.9%, $n = 5$, $P = .39$ compared with pre-injection values, paired t, $P < .0001$ compared with vehicle, RM-2W-ANOVA, Bonferroni). The same dose of SτAs (0.6 pmol) injected 15 min post LFS600 had no disruptive effect on successfully established LTD (SτAs post, 58.7 ± 10.8%, $n = 4$, $P = .034$ compared with pre-injection values, paired t, $P < .8624$ compared with vehicle, RM-2W-ANOVA, Bonferroni) (Fig. 1C, D). The potency of WT and P301S SτAs was very similar (Supplemental Fig. 1B, C).

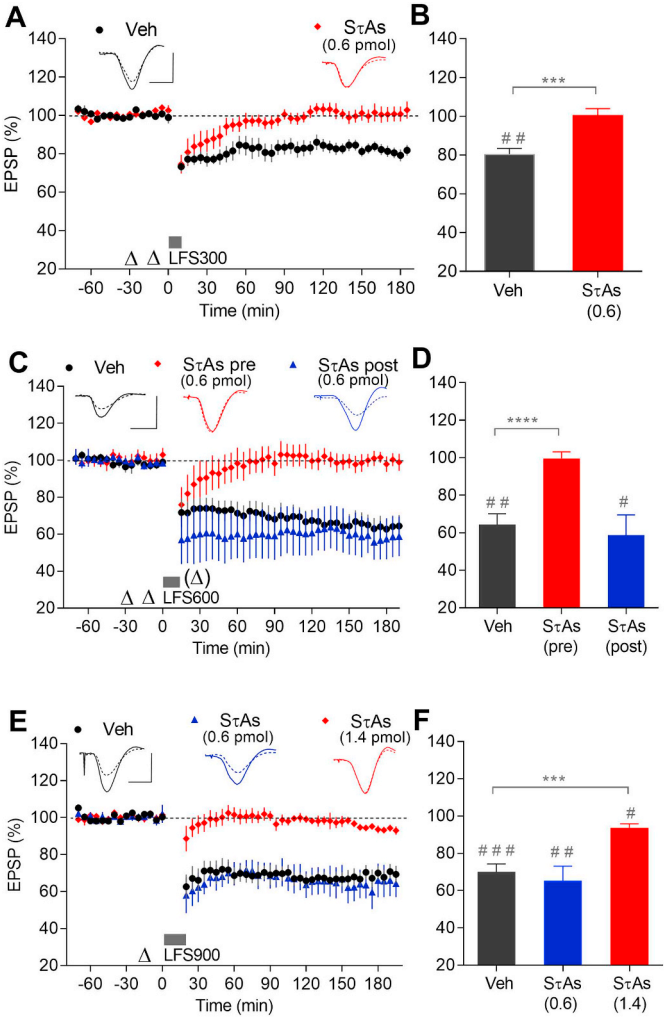

Fig. 1. Soluble tau aggregates potently inhibit LTD in the rat hippocampus *in vivo*.

SτAs inhibit LTD induction by 1 Hz conditioning stimulation consisting of either 300 (A, B) 600 (C, D) or 900 (E, F) pulses. (A, C, E) Time course of changes in synaptic field excitatory postsynaptic potentials (EPSPs) recorded in the CA1 area of anaesthetized rats. To induce LTD, the low-frequency stimulation protocol (LFS, denoted by horizontal bar at time 0, and number of pulses per protocol) was applied, with one exception, 15 min after intracerebroventricular (i.c.v.) injection (denoted by open triangle) of (A) vehicle (Veh, black circles, $n = 6$) or P301S SτAs (0.6 pmol, red diamonds, $n = 5$), (C) vehicle (Veh, black circles, $n = 5$) or 0.6 pmol SτAs (pre, red diamonds, $n = 6$) or (E) vehicle (Veh, black circles, $n = 7$) or equivalent doses of either P301S or WT SτAs (0.6 pmol, blue triangles, $n = 5$; 1.4 pmol, red diamonds, $n = 5$). One experimental group in (C) received 0.6 pmol P301S SτAs (post, blue triangles, $n = 4$) by i.c.v. injection (denoted by open triangle in parentheses) 15 min after LFS600. Insets are sample traces recorded 10 min prior to (solid line) and 3 h after LFS (dotted line). Scale bar, vertical 2 mV; horizontal 10 ms. (B, D, F) Summary bar charts showing the magnitude of LTD during the last 10 min for data in A, C, E. Numbers in brackets represent the SτA dose (in pmol). Values are mean ± SEM. $^{\#}P < .05$, $^{\#\#}P < .01$ or $^{\#\#\#}P < .001$ compared with pre-LFS, paired t-test; *** $P < .001$,**** $P < .0001$, two-way ANOVA with repeated measures followed by Bonferroni multiple comparison tests *versus* Veh group. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

We found that in order to effectively inhibit LTD when a stronger induction protocol (LFS900) was used, the dose of SτAs needed to be

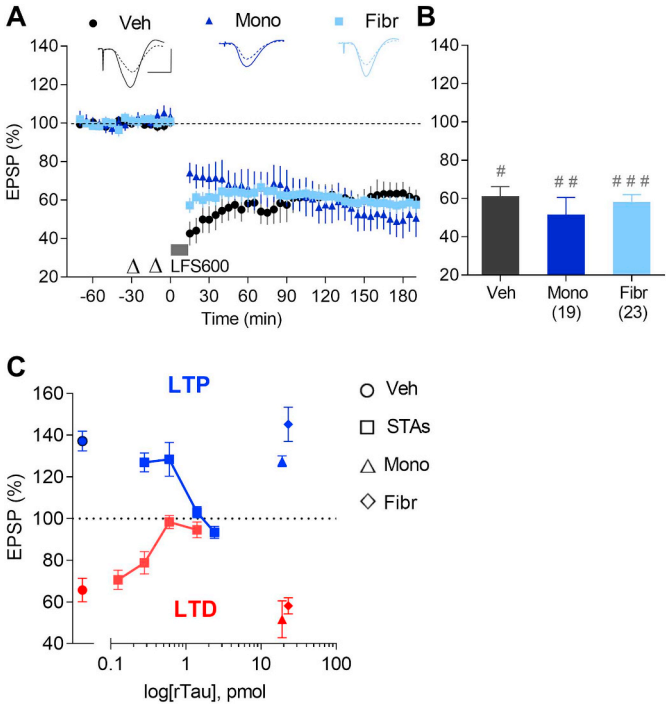

Fig. 2. Inhibition of LTD by tau is dependent on aggregation state.
(A) Time course graphs for the effects of vehicle (Veh, black circles, $n = 4$), P301S and WT tau monomers (Mono, 19 pmol, dark blue triangles, $n = 5$) or fibrils (Fibr, 23 pmol, light blue squares, $n = 5$) on the ability of LFS600 to induce LTD. (B) Summary of the magnitude of depression at 3 h in groups shown in (A). $^{\#}P < .05$, $^{\#\#}P < .01$ or $^{\#\#\#}P < .001$ (paired *t*-test).
(C) Dose-response relationship for the inhibition of either LTD (red) or LTP (blue) at 3 h after conditioning stimulation by different tau species. Vehicle (circles), SτAs (squares), tau monomers (triangles) and tau fibrils (diamonds). LTD was induced by LFS600. Data for LTP induced by 200 Hz stimulation are derived from Ondrejcak et al. (Ondrejcak et al., 2018). Data points for equivalent doses P301S and WT tau variants were combined. Values are the mean ± S.E.M. of 4–7 experiments. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

increased (Fig. 1E, F), even though the LTD triggered by either 600- or 900-pulse LFS appeared comparable in magnitude. Thus, application of LFS900 caused robust LTD in the vehicle group (Veh, 70.1 ± 4.3%, $n = 7$, $P = .0003$ compared with pre, paired *t*) and in animals injected with the same dose of SτAs that effectively blocked LTD-LFS600 (see Fig. 1C, D) (SτAs 0.6 pmol, 61.8 ± 14%, $n = 5$, $P = .0058$ compared with pre, paired *t*; $P = .8026$ compared with Veh, RM-2W-ANOVA, Bonferroni). When the dose of SτAs was increased to 1.4 pmol, LTD was again strongly inhibited (SτAs 1.4 pmol, 93.7 ± 2.1%, $n = 5$, $P = .0133$ compared with pre, paired *t*; $P = .0005$ compared with Veh, RM-2W-ANOVA, Bonferroni). This increased dose of SτAs also affected the initial phase of LTD immediately after application of LFS900. Thus, comparing first 10 min epochs after LFS900, the initial EPSP depression was significantly reduced in animals receiving 1.4 pmol dose of SτAs (91.6 ± 6%) compared to vehicle-treated group (64.9 ± 6.6%, $P = .0375$, one-way ANOVA, Bonferroni).

The inhibitory effect of tau on LTD, like that on LTP (Ondrejcak et al., 2018), was dependent on protein aggregation state (Fig. 2A, B). In contrast to SτAs, in animals injected with relatively high doses of either tau monomers (16–19 pmol) or fibrils (19–23 pmol) 15 min previously, the application of LFS600 triggered significant LTD (Mono, 51.6 ± 8.9%, $n = 5$, $P = .0048$ compared with pre, paired *t*; Fibr, 58.13 ± 3.9%, $n = 5$, $P = .0002$ compared with pre, paired *t*; RM-2W-ANOVA n.s. compared with Veh, 61.2 ± 5.1%, $n = 4$, RM-2W-ANOVA).

In summary, SτAs caused a dose-dependent inhibition of LTD which appeared be due to an increase in the threshold for LTD induction. Indeed, the potency of SτAs to inhibit LFS600-LTD was similar to what we found previously to be necessary to inhibit LTP induced by 200 Hz high frequency stimulation (HFS) (Ondrejcak et al., 2018) (Fig. 2C). In contrast, monomers and fibrils of tau did not significantly affect synaptic plasticity at doses considerably higher than the SτA doses required to fully block either LTD or LTP.

3.2. Cellular prion protein is required for tau-mediated inhibition of LTD

Previously we reported that LTP inhibition by SτAs is dependent on PrP^C (Ondrejcak et al., 2018), a putative receptor mediating the synaptic plasticity disrupting effects of Aßo (Freir et al., 2011; Lauren et al., 2009; Nicoll et al., 2013; Purro et al., 2018). Indeed, SτAs bind with high affinity to PrP (Corbett et al., 2018). Therefore, though Aßo and SτAs have opposite effects on LTD, we assessed the role of PrP^C in the tau-mediated inhibition of LTD using two monoclonal antibodies directed to different epitopes. Overall RM-2W-ANOVA comparing 5 groups confirmed significant effect of treatment with both anti-PrP antibodies on inhibition of LTD by soluble tau aggregates.

The anti-PrP antibody 6D11 targets residues within the putative primary PrP^C-Aßo binding site (aa ~95–110) and prevents inhibition of LTP by Aß (Hu et al., 2014; Lauren et al., 2009) and SτAs (Ondrejcak et al., 2018). Here, pre-treatment with 6D11 completely prevented the inhibition of LTD by SτAs (Fig. 3A, C). Thus, in animals that received injection of 6D11 (40 µg, i.c.v.) before separate i.c.v. injection of SτAs (0.6 pmol), the application of LFS600 triggered significant LTD, similar in magnitude to that induced in the vehicle-treated group (Vehicle, 49 ± 5.5%, $n = 5$, $P = .0005$ compared with pre, paired *t*; 6D11 + SτAs, 62.1 ± 7.9%, $n = 5$, $P = .014$ compared with pre, paired *t*; $P = .5694$ compared with vehicle, RM-2W-ANOVA, Bonferroni). On the other hand, LTD was strongly inhibited by SτAs in rats pre-treated with same dose of an isotype control antibody, (IgG2a + SτAs, 87.4 ± 7.3%, $n = 5$, $P = .1094$ compared with pre, paired *t*; $P < .0001$ compared with vehicle, $P = .005$ compared with 6D11, RM-2W-ANOVA, Bonferroni).

The other high-affinity anti-PrP antibody, MI-0131, is directed to the N-terminus of mature PrP (aa 23–51) (Ondrejcak et al., 2018). As with 6D11, we found that MI-0131 also prevented inhibition of LTD by SτAs (Fig. 3B, C). Thus, prior injection of MI-0131 (20 µg, i.c.v.) prevented the inhibition of LTD by SτAs (MI-0131 + SτAs, 66.7 ± 7.4%, $n = 5$, $P = .014$ compared with pre, paired *t*; $P = .1134$ compared with vehicle, RM-2W-ANOVA, Bonferroni) compared with the same dose of the IgG1 mAb 6E10 (6E10 + SτAs: 93.1 ± 2.8%, $n = 5$, $P = .1867$ compared with pre, paired *t*; $P < .0001$ compared with vehicle, $P = .0032$ compared with MI-0131, RM-2W-ANOVA, Bonferroni).

In summary, two antibodies to two different epitopes within the N-terminus of PrP abrogated the inhibition of LTD by soluble aggregates of tau. These findings provide strong evidence that PrP^C is crucial for tau-mediated disruption of LTD *in vivo*.

3.3. An antagonist of metabotropic glutamate receptor 5 fails to attenuate tau-mediated inhibition of LTD or LTP

Metabotropic glutamate receptors, in particular subtype 5 (mGlu5R), have been implicated in the synaptic plasticity disrupting actions of Aß *in vitro* (Li et al., 2009; Wang et al., 2005, 2009) and *in vivo* (Hu et al., 2014; Zhang et al., 2017). In particular, we found that an mGlu5R antagonist, MTEP, prevented Aß-facilitated LTD *in vivo* (Hu et al., 2014), consistent with the proposal that mGlu5R acts as a co-receptor with PrP^c for Aßo to trigger synaptotoxicity (Um et al., 2013). Given the PrP-dependence of the SτA-mediated inhibition of LTD in the present study, we wondered if mGlu5R was also required. As shown in Fig. 4A, MTEP failed to prevent the disruption of LTD by SτA. Thus, the application of LFS600 failed to induce LTD in animals administered

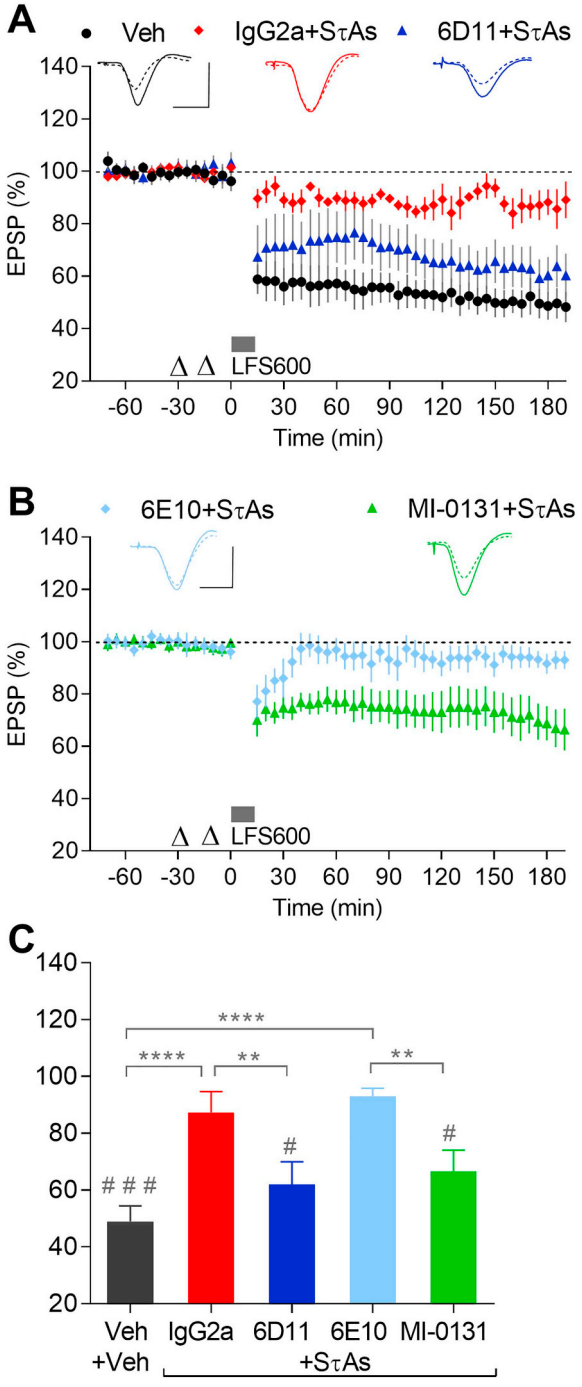

Fig. 3. Cellular prion protein is required for tau-mediated inhibition of LTD. (A) The effect of pre-injection of the anti-PrP mAb 6D11 i.c.v. on the ability of SτAs to inhibit LTD. Animals received i.c.v. injections of vehicle twice (Veh + Veh, black circles, $n = 5$), 6D11 mAb (40 μg) before 0.6 pmol P301S SτAs (6D11 + SτAs, blue triangles, $n = 5$) or IgG2a isotype control antibody (40 μg) followed by P301S SτAs (IgG2a + SτAs, red diamonds, $n = 5$). (B) Effect of pre-injection of the anti-PrP mAb MI-0131 on the ability of P301S SτAs to inhibit LTD. Animals were pre-treated with 20 μg MI-0131 (MI-0131 + SτAs, green triangles, $n = 5$) or the control mAb 6E10 (6E10 + SτAs, light blue diamonds, $n = 5$). (C) Values at 3 h post-LFS from A, B. $^{\#}P < .05$, $^{\#\#\#}P < .001$ (paired *t*-test); $^{**}P < .01$ $^{****}P < .0001$ (RM-2W-ANOVA, Bonferroni *post-hoc* test). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

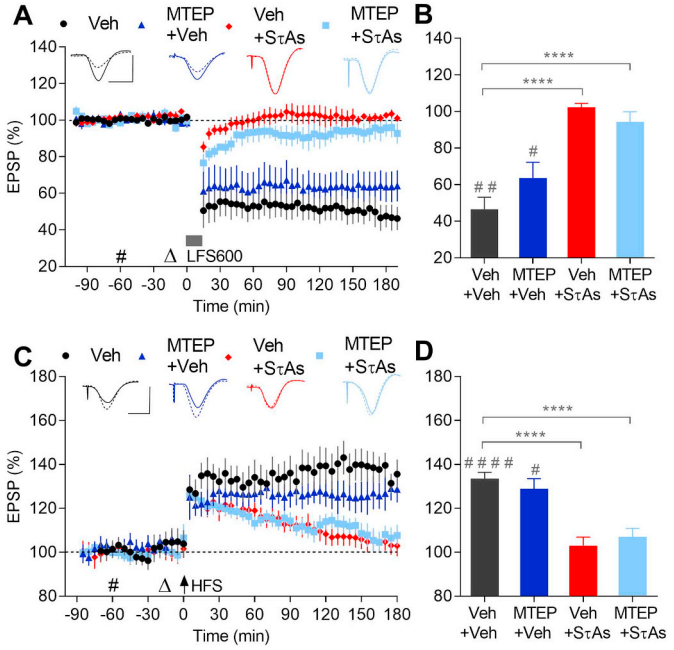

Fig. 4. Tau-mediated inhibition of LTD and LTP is not blocked by an antagonist of subtype 5 metabotropic glutamate receptor.
(A) Effect of systemic (i.p.) injection of the mGlu5R negative allosteric modulator MTEP on SτA-mediated inhibition of LTD. Animals received injections i.p. (shown as hash symbol) 45 min before i.c.v. (shown as open triangle) injection for vehicle (Veh + Veh, black circles, $n = 5$), MTEP (3 mg/kg) before Veh (MTEP + Veh, dark blue triangles, $n = 5$), vehicle before 0.6 pmol P301S SτAs (Veh + SτAs, red diamonds, $n = 5$) or MTEP (3 mg/kg) before P301S SτAs (MTEP + SτAs, light blue squares, $n = 5$). (B) Values at 3 h post-LFS from A. (C) Effect of MTEP (3 mg/kg, i.p.) on SτA-mediated inhibition of HFS-induced LTP. Animals received injections of vehicle twice (Veh + Veh, black circles, $n = 6$), MTEP before Veh i.c.v. (MTEP + Veh, dark blue triangles, $n = 4$), vehicle before 1.2 pmol P301S SτAs (Veh + SτAs, red diamonds, $n = 8$) or MTEP (3 mg/kg) before P301S SτAs (MTEP + SτAs, light blue squares, $n = 7$). (D) Values at 3 h post-HFS from C. $^{\#}P < .05$, $^{\#\#}P < .01$, $^{\#\#\#\#}P < .0001$ (paired *t*-test); $^{****}P < .0001$ (RM-2W-ANOVA, Bonferroni post-hoc test) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

MTEP systemically (3 mg/kg, i.p.) before i.c.v. injection of SτAs (0.6 pmol) (MTEP + SτAs, 94.4 ± 5.5%, $n = 5$, $P = .2032$ compared with pre, paired *t*; $P < .0001$ RM-2W-ANOVA, Bonferroni, compared with vehicle group, Veh, 46.5 ± 6.6%, $n = 5$, $P = .0004$ compared with pre, paired *t*). Moreover, the same dose of MTEP had no effect on control LTD induced by LFS600 (MTEP + PBS, 63.8 ± 8.4%, $n = 5$, $P = .02$ compared with pre, paired *t*; $P = .9776$ compared with vehicle, RM-2W-ANOVA, Bonferroni). Similarly, basimglurant, a potent and highly selective mGlu5R negative allosteric modulator (Jaeschke et al., 2015), did not prevent LTD inhibition by SτAs (90.1 ± 4%, $n = 3$, $P = .2172$ compared with pre, paired *t*).

Because this finding was somewhat surprising, we decided to determine if the ability of SτAs to disrupt LTP, like LTD, did not require mGlu5R (Fig. 5B, C). The dose of SτAs was increased to 1.4 pmol, i.c.v. in order to robustly inhibit LTP induced by 200 Hz HFS (Ondrejcak et al., 2018) (also see Fig. 2C). Consistent with our previous report, this dose of SτAs preferentially inhibited LTP magnitude after ~1 h post-HFS in vehicle-pretreated animals (Veh + SτAs, 103.1 ± 8.4%, $n = 8$, $P = .5561$ compared with pre, paired *t*; $P < .0001$ compared with vehicle, RM-2W-ANOVA, Bonferroni). Moreover, the same HFS

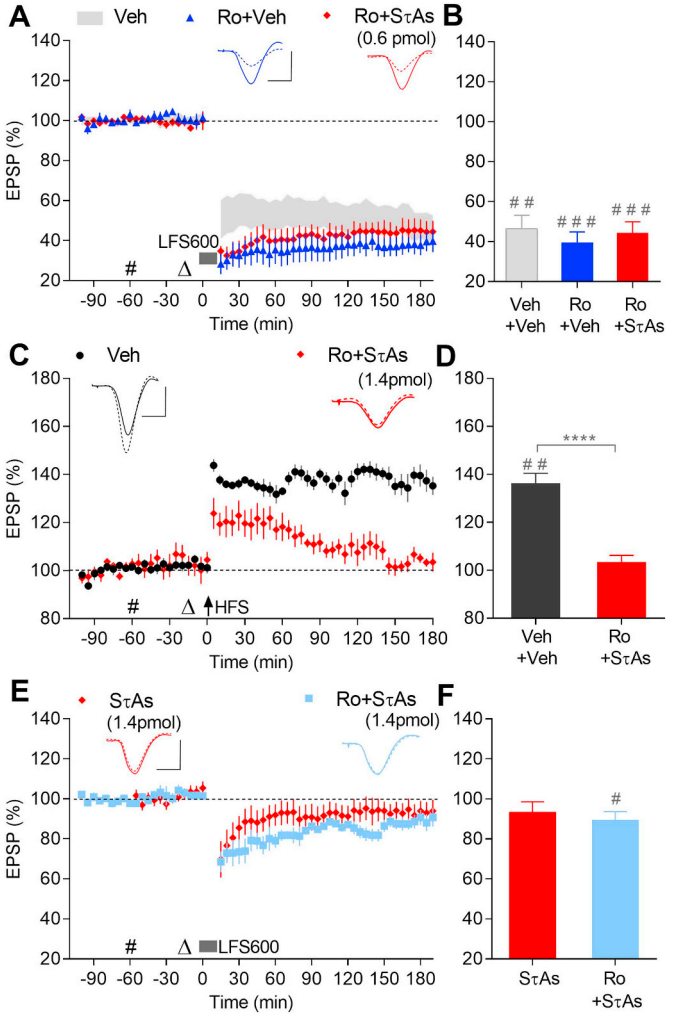

Fig. 5. Tau-mediated inhibition of LTD, but not LTP, is prevented by a GluN2B NMDA receptor antagonist.

(A) Effect of the systemic administration of the non-competitive GluN2B-selective antagonist (Ro 25–6981) on SτA-mediated inhibition of LTD. Animals received Ro 25–6981 (12 mg/kg, i.p.) followed by an i.c.v. injection of either vehicle (Ro + Veh, dark blue triangles, $n = 5$) or 0.6 pmol P301S SτAs (Ro + SτAs, red pyramids, $n = 5$) before the application of LFS600. Control group (animals receiving two injections of vehicle, Veh, greyed out trace, $n = 5$) is the same as shown in Fig. 4A. (B) Values at 3 h post-LFS from A. (C) Effect of the same dose of Ro 25–6981 on the ability of P301S SτAs (1.4 pmol, i.c.v.) (Ro + SτAs, red diamonds, $n = 5$) to inhibit HFS-induced LTP. Controls received two injections of vehicle (Veh + Veh, black circles, $n = 5$) before the application of HFS. (D) Values at 3 h post-HFS from C. (E) Time-course graph of groups injected with the higher dose of SτAs (1.4 pmol, i.c.v.) either alone (SτAs, red diamonds, $n = 5$) or 45 min after Ro 25–6981 (12 mg/kg, i.p.) (Ro + SτAs, light blue squares, $n = 6$). (F) Values at 3 h post-LFS from E. $^{\#}$ $P < .05$, $^{\#\#\#}$ $P < .001$ (paired t-test); **** $P < .0001$ (RM-2W-ANOVA, Bonferroni post-hoc test) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

protocol failed to induce significant LTP in animals injected with MTEP (3 mg/kg, i.p.) followed by SτAs (MTEP + SτAs, 107.1 ± 3.8%, $n = 7$, $P = .4735$ compared with pre, paired t; $P < .0001$ compared with vehicle, RM-2W-ANOVA, Bonferroni). This dose of MTEP also did not affect control LTP (MTEP + Veh, 128.9 ± 4.7%, $n = 4$, $P = .0017$ compared with pre, paired t; $P = .8303$ RM-2W-ANOVA, Bonferroni, compared with vehicle group, Veh, 133.5 ± 2.8%, $n = 6$, $P < .0001$ compared with pre, paired t).

Taken together, the findings that MTEP did not prevent the inhibition of either LTP or LTD by SτAs indicates that unlike Aβo, mGlu5Rs are unlikely to be involved in the synaptic plasticity disrupting action of soluble tau aggregates.

3.4. A GluN2B NMDA receptor antagonist reduces tau-mediated inhibition of LTD, but not LTP

Apart from mGlu5Rs, NMDARs containing GluN2B subunits are particularly implicated in Aß-mediated synaptic plasticity disruption (Hu et al., 2009; Li et al., 2011) and have again been implicated in PrP-dependent mechanisms of synaptotoxicity (Um et al., 2012). First, we tested the GluN2B-selective negative allosteric modulator Ro 25–6981 (Fischer et al., 1997) to prevent SτA-mediated LTD inhibition (Fig. 5A, B). Ro 25–6981 prevented SτA-mediated inhibition of LTD induced by LFS600. Although the initial level of depression in the first 45 min post-LFS appears slightly greater in the presence of Ro 25–6981 alone (12 mg/kg, i.p. 1 h pre-LFS), there was no significant difference in the magnitude of LFS600-induced LTD at 3 h between the three groups (Ro + Veh, 39.7 ± 5.2%, $n = 5$, $P = .0003$ compared with pre, paired t; RM-2W-ANOVA n.s., compared with Veh group; Ro + SτAs, 0.6 pmol, 44.4 ± 5.6%, $n = 5$, $P = .0008$ compared with pre, paired t; RM-2W-ANOVA n.s., compared with Veh group) (Fig. 5A, B), consistent with our previous report that this dose of Ro 25–6981 did not prevent LFS900-induced LTD (O'Riordan et al., 2018).

Next, we examined the ability of the same dose of Ro 25–6981 to prevent LTP disruption by SτAs (Fig. 5C, D). Intriguingly, systemic pretreatment with Ro 25–6981 (12 mg/kg, i.p.) did not abrogate the inhibition of LTP by SτAs (1.4 pmol, i.c.v., see Fig. 4C) (Ro + SτAs, 103.4 ± 2.8%, $n = 5$, $P = .6989$ compared with pre, paired t; $P < .0001$ RM-2W-ANOVA, Bonferroni, compared with Veh group, 136.3 ± 4.1%, $n = 5$, $P = .0028$ compared with pre, paired t) (Fig. 5C, D).

Because the dose of SτAs required to inhibit LTP was higher than that (0.6 pmol, i.c.v.) used to inhibit LFS600-induced LTD, we wondered if the sensitivity of LTD inhibition to GluN2B antagonist was dependent on the dose of SτAs. Therefore we tested the ability of Ro 25–6981 to prevent the inhibition of LTD by 1.4 pmol (i.c.v.) SτAs (Fig. 5E, F). This higher dose also blocked LFS600-induced LTD (Veh + SτAs, 93.5 ± 5.6%, $n = 5$, $P = .0883$ compared with pre, paired t). Even though LFS600 induced a small LTD in animals that had been previously injected with Ro 25–6981 followed by SτAs (1.4 pmol) (Ro + SτAs, 89.4 ± 4.2%, $n = 6$, $P = .02$ compared with pre, paired t) there was no significant difference compared with animals receiving relatively high-dose SτAs alone (RM-2W-ANOVA, n.s.).

Taken together, these findings indicate that whereas GluN2B-containing NMDARs are required for LTD inhibition by relatively low dose SτAs, blocking these receptors failed to reduce either LTD or LTP inhibition by a higher dose of SτAs.

3.5. SτAs modulate the disruptive effects of Aß on LTP and LTD

Given the shared ability of both Aß (Nicoll et al., 2013) and SτAs (Ondrejcak et al., 2018) to inhibit LTP in a PrP-dependent manner we decided to determine if, at subthreshold doses of tau and Aß soluble species that alone cause no significant synaptic plasticity impairment could inhibit LTP when administered in combination (Fig. 6A, B). Animals were injected with relatively low doses of SτAs (0.25 pmol, see Fig. 2C) or soluble Aß (ADDLs, 0.14 nmol; see (Zhang et al., 2016)) alone or together. Neither SτAs nor Aß affected the induction of LTP when injected alone at these low dose levels (Aß, 130.2 ± 2.5%, $n = 5$, $P = .0007$ compared with pre, paired t; SτAs, 127.2 ± 4.6%, $n = 7$, $P = .0023$ compared with pre, paired t; $P = .6816$ *or* $P > .9999$, respectively in RM-2W-ANOVA, Bonferroni, compared with Veh group). By contrast, in interleaved experiments, application of HFS in animals that received two separate injections (i.c.v.) prior to conditioning stimulation, LTP was significantly inhibited compared to vehicle treated animals (SτAs + Aß, 99.1 ± 3%, $n = 5$; $P = .9832$

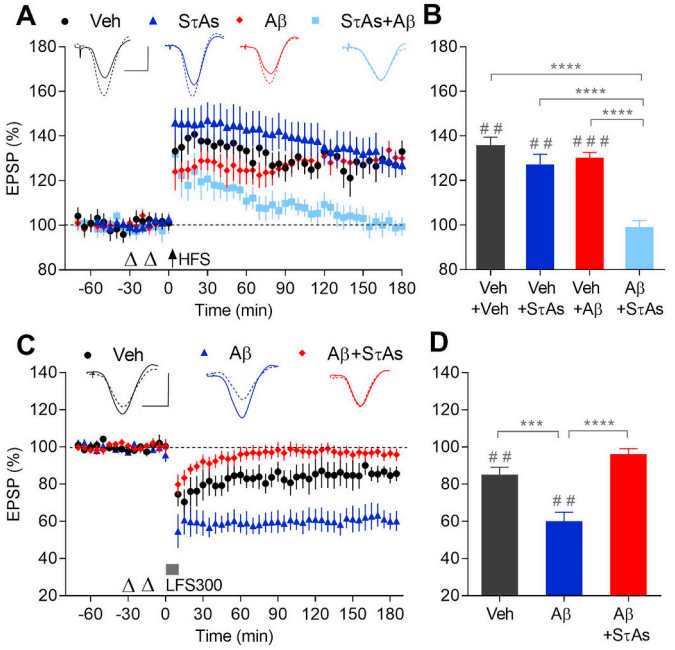

Fig. 6. SτAs modulate the disruptive effects of soluble Aß on LTP and LTD. (A) A low dose of SτAs lowers the threshold for Aß to inhibit LTP. Rats received i.c.v. injections of vehicle (Veh, black circles, $n = 5$) or sub-threshold doses of either P301S SτAs (0.25 pmol, dark blue triangles, $n = 7$) or Aß (ADDLs, 0.14 nmol, red diamonds, $n = 5$). For the combination treatment, animals received the same doses of Aß and SτA in two separate injections prior to HFS (Aß + SτA, light blue squares, $n = 5$). (B) Summary of data in A at 3 h. (C) SτAs prevent Aß-facilitated LTD. Animals received i.c.v. injection of either vehicle (Veh, black circles, $n = 5$), Aß only (Aß, 1.17 nmol, dark blue triangles, $n = 5$) or two separate injections of Aß (1.17 nmol) and P301S/WT SτA (0.6 pmol, a dose that strongly blocks LFS300-induced LTD, see Fig. 1A, B) in random order (Aß + SτAs, red diamonds, $n = 6$) before applying the weak induction protocol, LFS300. (D) Values at 3 h post-LFS from C. $^{\#\#}P < .01$, $^{\#\#\#}P < .001$ (paired *t*-test); *** $P < .001$,**** $P < .0001$ (RM-2W-ANOVA, Bonferroni post-hoc test). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

compared with pre, paired *t*, $P < .0001$ RM-2W-ANOVA, Bonferroni, compared with Veh, 135.8 ± 3.6%, $n = 5$; $P = .0067$ compared with pre, paired *t*).

With regard to LTD, Aß (Hu et al., 2014) and SτAs (the present studies) have opposite effects even though both of these effects are PrP-dependent. The question arises which action predominates. Using the relatively weak LFS300 conditioning protocol we confirmed the finding of Hu et al. (Hu et al., 2014) that Aß (1.17 nmol, i.c.v.) facilitated LTD (Veh, 85.2 ± 4%, $n = 5$, $P = .0015$ compared with pre, paired *t*; Aß, 60.1 ± 4.9%, $n = 5$, $P = .0014$ compared with pre, paired *t*, $P = .0002$ compared with Veh, RM-2W-ANOVA, Bonferroni) (Fig. 6C, D). In contrast, LFS300 failed to induce LTD in animals receiving a separate injection of SτAs (0.6 pmol, a dose that strongly blocks LFS300-induced LTD, see Fig. 1A, B) in addition to Aß, regardless of the injection sequence (Aß + SτAs, 96.2 ± 2.9%, $n = 6$, half the animals receiving SτAs first and the other half getting Aß first; $P = .5022$ compared with pre, paired *t*; $P = .1229$ RM-2W-ANOVA, Bonferroni, compared with Veh group and $P < .0001$ *vs* Aß alone).

Because supra-threshold doses of these agents may act *via* different mechanisms to affect LTD, we also tested a combination of subthreshold doses of the peptides on the ability of LFS300 to induce LTD. Consistent with our findings shown in Figs. 1A and 6C, this stimulation protocol triggered a small but significant LTD in vehicle-injected animals (Veh, 85.2 ± 0.9%, $n = 4$, $P = .0147$ compared with pre, paired *t*) (Fig. S2A, B). We chose a dose of SτAs (0.25 pmol) that was half the minimum effective dose required to inhibit LFS600-induced LTD (see Fig. 2C) and a dose of Aß (0.14 nmol) that did not affect LTP (see Fig. 6A, B). Overall, there was no significant effect (RM-2W-ANOVA, n.s.) of these doses of SτAs (alone, 89.2 ± 4.1%, $n = 4$), soluble Aß (alone, 91.8 ± 4.3%, $n = 4$) or in combination (SτAs + Aß, 96.1 ± 3.5%, $n = 5$) (Supplemental Fig. 2A, B).

These findings indicate that whereas subthreshold amounts of Aß and tau appear to co-ordinately facilitate inhibition of LTP, this was not the case for LTD. Also, the ability of Aßo to lower the LTD induction threshold is completely overridden by SτA-mediated LTD inhibition.

4. Discussion

Here we report that, in addition to inhibiting LTP, soluble aggregates of tau, but not monomers or fibrils, potently increased the threshold for LTD induction in the rat hippocampus *in vivo*. Similar to LTP inhibition by SτAs, SτA-mediated LTD inhibition required cellular prion protein. Although block of the putative PrP^c coreceptor mGlu5R did not prevent the disruption of synaptic plasticity, a selective antagonist at GluN2B subunit-containing NMDARs reduced SτA-mediated inhibition of LTD but not LTP. Intriguingly, whereas a positive interaction between subthreshold doses of Aßo and SτAs characterized their inhibition of LTP, SτAs completely blocked Aßo-facilitated LTD.

Previously, we and others reported that SτAs, but not tau monomers or fibrils, rapidly inhibited LTP both *in vitro* (Fa et al., 2016; Puzzo et al., 2017) and *in vivo* (Ondrejcak et al., 2018). Here, we extended this tau aggregation-state selective rapid disruption of hippocampal synaptic plasticity to LTD *in vivo*. The doses used do not affect baseline excitatory synaptic field potentials or paired pulse facilitation (Ondrejcak et al., 2018) so are unlikely to be caused by a general disruption of neurotransmitter release, such as has been found after intracellular injection of certain tau preparations (Moreno et al., 2016). The high potency of soluble aggregates of tau, and superior ability over monomers and fibrils, to rapidly disrupt synaptic plasticity is attributable to the diversity in kinetics and inherent synaptotoxicity of the different assemblies (Medina and Avila, 2014; Ondrejcak et al., 2018). Thus, a relatively high affinity for putative 'toxic receptors' may help account for the greater activity of SτAs, though other factors (such as relative ease of diffusion and resistance to clearance mechanisms) are likely to contribute. The ~2-fold higher potency of SτAs to inhibit LFS600-induced LTD found here compared with 200 Hz-induced LTP (Ondrejcak et al., 2018) may be because LFS600 is closer to the LTD induction threshold than the 200 Hz protocol is for LTP induction. Indeed, increasing the number of pulses from 600 to 900 pulses during the 1 Hz conditioning stimulation required higher doses of SτAs to inhibit LTD, and application of SτAs soon after LFS600 did not reverse LTD. These findings strongly indicate that SτAs increase the threshold for LTD induction. Disruption of the early phase of both LTD (this study) and LTP (Ondrejcak et al., 2018) appears to require higher concentrations of SτAs. However, unlike LTD, increasing the strength of the induction protocol does not overcome the inhibition of LTP by SτAs (Ondrejcak et al., 2018). It therefore seems likely that different or additional sites of action may be engaged to mediate the disruptive effects of SτAs on the mechanisms underlying the induction and expression of synaptic plasticity with increasing concentrations.

Based on the known ability of Aßo to inhibit LTP and facilitate LTD in a PrP-dependent manner (Hu et al., 2014; Nicoll et al., 2013), and our previous findings that different tau preparations also cause PrP-dependent inhibition of LTP (Hu et al., 2018; Ondrejcak et al., 2018), we hypothesized that SτAs would act in a similar manner to Aßo and facilitate LTD. Contrary to our prediction, SτAs inhibited LTD, but this opposite effect of SτAs on LTD was also PrP-dependent. The finding that the inhibition of LTD by SτAs was blocked by pre-treatment with two monoclonal antibodies directed to the two putative Aßo binding sites in PrP residues (23–33 and 88–111) is consistent with our previous findings on LTP inhibition (Ondrejcak et al., 2018) and recent data indicating SτAs bind with high affinity to PrP at both these sites (Corbett

et al., 2018). It appears therefore that even though SτAs and Aß exert opposite effects on LTD, they bind to PrP in a similar manner. The question arises as to what might be the basis of this apparent paradox.

In the case of Aßo binding to PrP, recently the interaction at the two sites on PrP has been reported to transform part of the highly flexible N-terminal region into an α-helical structure and to generate a semi-stable PrP^c-Aßo hydrogel complex that promotes coupling of PrP^c to mGlu5R (Kostylev et al., 2018). Because PrP^c does not have a transmembrane domain, being anchored on the cell surface *via* the glycolipid glycophosphatidylinositol, linkage through mGlu5R is believed to be essential to trigger downstream synaptotoxicity (Brody and Strittmatter, 2018). Indeed, the mGlu5R antagonist MTEP prevents both the inhibition of LTP and facilitation of LTD by Aß (Hu et al., 2014). However, in the present studies the same dose of MTEP failed to abrogate the inhibition of either LTP or LTD by SτAs. Notwithstanding the limitations to interpreting the lack of effect of pharmacological interventions, it seems likely that even though these protein aggregates appear to bind to similar sites on PrP, the coupling of the ligand-bound PrP^c to mGlu5R and related effector mechanisms appears to be different for Aß and SτAs. These findings also raise the question as to whether very different synaptotoxic mechanisms arise downstream of PrP binding, perhaps by engaging a different co-receptor.

Apart from mGlu5R, GluN2B subunit-containing NMDARs have been implicated as major contributors to synaptic plasticity-disrupting effects of Aßo, including those mediated *via* PrP-dependent mechanisms (Um et al., 2012). In particular, GluN2B-selective antagonists appear to block Aßo-mediated inhibition of LTP more effectively than Aßo-facilitated LTD (Hu et al., 2009; Hu et al., 2014). In contrast, our present findings indicate that SτA-mediated inhibition of LTD is more sensitive than LTP inhibition to the beneficial effect of the GluN2B antagonist. Thus, the inhibition of LTD, but not LTP, by SτAs was abrogated by Ro 25–6981. Because systemic treatment with this relatively high dose of Ro 25–6981 may not effectively block all GluN2B subunits, in particular those found in triheteromeric NMDARs (France et al., 2017), we cannot rule out the possibility that Ro 25–6981-resistant GluN2B subunits contribute to LTP inhibition by SτAs.

Alternative shared mechanisms for soluble Aß and tau aggregate-mediated inhibition of LTP include a requirement for APP (Puzzo et al., 2017) and phospholipase D1 but not D2 (Krishnan et al., 2018). If or how these mechanisms relate to the PrP-dependent inhibition of LTD by soluble tau is unclear. The forms of LTP and LTD studied *in vivo* here are both NMDAR-dependent (Hu et al., 2014; Kumar, 2011; Luscher and Malenka, 2012). Indeed, although systemic administration of Ro 25–6981 does not significantly alter the control forms of LTD or LTP (but see (Fox et al., 2006)) studied here, local intrahippocampal injection attenuates 100 Hz -induced LTP and “paired burst” -induced LTD (Fox et al., 2006), and i.c.v. injection blocks LFS-900 -induced LTD (O'Riordan et al., 2018) *in vivo*. Therefore, one plausible explanation as to why both forms of synaptic plasticity were inhibited by SτAs is that NMDAR-mediated transmission was reduced. Although we have no direct evidence, the apparent reduction in the initial extent of depression following the LFS, especially with higher doses of SτAs, and potentiation following the HFS (Ondrejcak et al., 2018) is consistent with this suggestion. Indeed, acute treatment with recombinant full-length tau recently has been reported to potently inhibit NMDAR-mediated activation of MAP kinase in hippocampal neurons (Franco et al., 2018).

Clearly a reduction in both LTP and LTD will greatly limit the dynamic range of synaptic plasticity in the hippocampal CA1 area. Although inhibition of LTP is by far the best-established model for synaptic plasticity mechanisms underlying cognitive impairment, LTD disruption is also likely to play an important role (Connor and Wang, 2016; Kemp and Manahan-Vaughan, 2004). Furthermore, although the promotion of LTD-like ‘synaptic weakening’ mechanisms by Aßo has been proposed as a basis for the inhibition of LTP and later synaptic loss in AD (Sheng et al., 2012; Whitehead et al., 2017), this does not appear to be the case with SτAs. Importantly, SτAs potently prevented Aß-facilitated LTD. As a consequence, when ‘synaptic weakening’ mechanisms are enhanced by synaptotoxic Aßo it is likely that these will be greatly suppressed if and when certain synaptotoxic forms of tau aggregates are also present. Thus, even though LTP inhibition by Aß requires endogenous tau (Shipton et al., 2011), the present findings indicate that when certain soluble aggregates of tau and Aß are present together tau will not only facilitate but also will oppose different synaptic plasticity disrupting actions of Aß. Indeed, such complex interactions of tau and Aß at synapses may contribute to the insidious progression of AD. Clearly, future research should try to determine how representative artificially prepared soluble aggregates of recombinant full-length tau are of the many different soluble tau species likely to be present in the interstitial fluid of AD brain and their long-term effects on synaptic plasticity (Fa et al., 2016; Hu et al., 2018; Lasagna-Reeves et al., 2011; Ondrejcak et al., 2018; Sato et al., 2018). Previous research, for example, reported that prolonged exposure to raised levels of endogenous disease-associated phosphorylated tau in transgenic mice can cause a reversible inhibition of hippocampal LTD in the absence of a deficit in LTP (Ahmed et al., 2015). Thus, with chronic exposure to endogenously generated synaptotoxic protein species homeostatic mechanisms are likely to control the relative sensitivity of LTP and LTD mechanisms to disruption (Chakroborty et al., 2012; Huh et al., 2016) and their role in disease-relevant synaptic loss or neurodegeneration.

In conclusion, the present finding that LTD inhibition by SτAs is blocked by anti-PrP antibodies firmly supports a critical role of PrP^c in mediating the synaptotoxicity of soluble tau aggregates *in vivo*. Thus, targeting PrP^c may prove an attractive strategy in early AD to slow disease pathogenesis by reducing synaptic plasticity disruption by soluble species of tau, but also Aß and possibly α-synuclein (Corbett et al., 2018; Ferreira et al., 2017; Urrea et al., 2018), other key AD-associated proteins that engage PrP^c, even though the subsequent downstream mechanisms of synaptotoxicity may diverge significantly.

Funding

This research was supported by AstraZeneca, Science Foundation Ireland (14/IA/2571) and the Irish Health Research Board (HRA-POR-2015-1102) to M.J.R and National Natural Science Foundation of China (81471114) to N.-W.H.

Conflicts of interest

None. G.F., M.S.P. and A.B. are employees and shareholders of AstraZeneca.

Author contributions

T.O. and N.-W.H. performed the experiments, G.T.C. and G.F. prepared and characterized recombinant tau, T.O. and M.J.R. wrote the manuscript, all the authors contributed to study design and editing of the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nbd.2019.03.022.

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