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Hippocampal synaptic plasticity in neurodegenerative diseases: Aß, tau and beyond

https://doi.org/10.1515/nf-2017-A063

Abstract: The study of long-term potentiation (LTP) and long-term depression (LTD) in disease models provides essential mechanistic insight into synaptic dysfunction and remodelling in many neuropsychiatric and neurological illnesses. The ability of misfolded forms of the two key proteins of Alzheimer's disease, amyloid ß (Aß) and the microtubule binding tau to disrupt hippocampal synaptic plasticity, engender highly sensitive litmus tests of impending synaptic failure and subsequent structural pathology. Many transgenic and injection-induced rodent models show rapid and persistent inhibition of LTP, and sometimes opposing effects of Aß and tau on LTD. Intriguingly, both intracellular and extracellular actions of these proteins are implicated. Both directly targeting these proteins and abrogating their synaptotoxic actions are being explored to redress the insidious shift from physiological to pathological plasticity in early Alzheimer's disease.

Keywords: Alzheimer's disease, Neurodegeneration, Synaptic toxicity, Long-term potentiation; Long-term depression

Introduction

The disruption of the function of synapses is a major contributor to most neuropsychiatric and neurodegenerative illnesses, classifying them as 'synaptopathies' often including structural changes at the synapse. In the case of most neurodegenerative diseases synaptopathy likely long presages the death of neurons (Overk and Masliah, 2014). Indeed glutamatergic synaptic loss is the most proximate structural correlate of clinical dementia in Alzheimer's disease (AD) (Terry et al., 1991), one of the most common neurodegenerative disorders accounting for more than half of dementia cases (German Alzheimer Society, https://www.deutsche-alzheimer.de).

Although typical AD is late-onset (loAD), an earlier familial form of AD (fAD) with an incidence of less than 0.5 % develops between 30 and 50 years of age. fAD is caused by mutations in three genes, amyloid precursor protein (*APP*), presenilin 1 (*PSEN1*) and presenilin 2 (*PSEN2*). Research of the last decade has revealed that loAD is triggered by a complex interaction of environmental and genetic risk factors, including *APOE*e4, a variant of the gene encoding apolipoprotein E lipid binding proteins, and more than 20 other genes that each confer a small AD risk.

What drives this synaptic dysfunction and damage in AD? One well-recognized means of investigating this question is to evaluate synaptic plasticity: the activity-dependent persistent functional up- or down- regulation of transmission between neurons. The two important and most frequently investigated forms of synaptic plasticity are long-term potentiation, a long-lasting increase in synaptic transmission, and long-term depression, a long-lasting decrease of the latter. Although LTP and LTD can be induced by a variety of electrical and chemical protocols, a short high-frequency stimulation (HFS, e. g. 100 Hz for 1sec) is typically used to induce LTP, while long trains of low-frequency stimulation (LFS, e. g. 1 Hz for 15 min) are employed to generate LTD. These typical electrical induction protocols result in depolarization of the postsynaptic membrane and in the displacement of the Mg^{2+}-block of the ion channel of postsynaptic NMDA-receptors (NMDARs), allowing for strong (by HFS) or moderate (by LFS) calcium influx into the neuron. Strong calcium influx activates multiple protein kinase signalling cascades which, in turn, operate an increase in channel conductance of AMPA-receptors (AMPARs), a subtype of glutamate receptors responsible for fast synaptic responses. Parallel to this, the insertion of additional AMPARs into the postsynaptic membrane is triggered. Both mechanisms cause synergistically a long-lasting increase in synaptic transmission, i. e. LTP.

A moderate long-lasting influx of calcium evoked by LFS, in contrast, activates protein phosphatase signalling cascades, resulting in a decrease in the number of postsynaptic AMPARs by internalization into the cytoplasm, and hence, in reduced synaptic transmission and LTD.

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Some studies point to an involvement of presynaptic processes in some forms of LTP and LTD. However, a detailed description of all these processes is beyond the scope of this review and we refer to the reviews by Collingridge *et al.* 2010, Luscher and Malenka, 2012 and Bliss *et al.* (in this issue) for further reading.

Different forms of LTP and LTD are found at excitatory and inhibitory synapses throughout the brain and mediate key brain functions including certain forms of memory. A preponderance of studies supports the hypothesis of LTP representing a model mechanism for learning and memory formation at the cellular level (see Bliss *et al.* in this issue). However, there is increasing evidence in recent years that also LTD serves as a mechanism for memory formation (Kemp and Manahan-Vaughan, 2007; Collingridge et al., 2010; Dong et al., 2013; Scullion et al., 2018). Disruption of LTP or LTD can be extremely sensitive indicators of incipient synaptic failure that can be investigated both *in vivo* and *in vitro*. While a pathological impairment of LTP or LTD *in vivo* provides information about systems modulation and circuit-level changes in the relatively intact system, the investigation of both forms of synaptic plasticity *in vitro* is a powerful means to assess detailed cellular/molecular mechanisms. Since LTP- and LTD-like mechanisms seem to be involved in different forms of learning, which also depend on the brain region, the study of both forms of synaptic plasticity could provide valuable complementary insights into impaired synaptic functions.

Although deficits in LTP-like cortical plasticity have been found in patients with AD (Koch et al., 2012), researchers rely on available animal models to probe synaptic plasticity in susceptible pathways, especially the hippocampal network. Investigations of synaptic plasticity in different models have provided some of the seminal discoveries in AD research over the last two decades.

Amyloid ß (Aß) and plasticity

The deposition of extracellular amyloid plaques, consisting of water-insoluble misfolded fibrillary Aß, is one major histological hallmark of AD. Amyloidogenic Aß peptides are derived by sequential enzymatic cleavage of APP by different secretases, with Aß42 being the dominant neurotoxic agent. We discovered about 20 years ago that Aß rapidly and potently inhibited hippocampal LTP (Cullen et al., 1997) (Figure 1A) and facilitated LTD (Kim et al., 2001) at CA3-to-CA1 synapses after intracerebral injection in anaesthetized rats *in vivo*, implicating plasticity disruption by Aß in the synaptopathy of AD. It is particularly valuable to determine the synaptic plasticity disruptive effects of exogenously applied patient-derived samples in addition to APP and PSEN transgenic animals. Even though synaptic plasticity also is often disrupted in transgenic APP mice (Chapman et al., 1999) and related models, it is difficult to determine if Aß is the culprit (Sasaguri et al., 2017). The development of new knock-in APP mouse models (Sasaguri et al., 2017) and low gene dose APP transgenic and virally transduced rats (Audrain et al., 2017; Qi et al., 2014) are helping to address at least some of these complex issues.

The key question of which forms of Aß are the most synaptotoxic is a matter of intense investigation (Benilova et al., 2012). Pre-fibrillar soluble Aß oligomers ($Aß_o$s) vary in size from dimers to much larger assemblies, including protofibrils of thousands of Aß molecules (Lee et al., 2017). Whereas natively unfolded monomers of Aß appear inactive, low-n $Aß_o$s, (Aβ oligomers resulting from the aggregation of two or several Aβ molecules), that are derived from soluble AD brain extracts are potent disrupters of synaptic plasticity (Yang et al., 2017). In apparent contrast, pure synthetic Aß dimers need to aggregate to become potent synaptotoxins. Regardless of size, Aß conformation appears to be critical in triggering dysfunction.

Until recently, most researchers assumed that soluble aggregates of Aß are the most synaptotoxic products of APP metabolism. To many people's surprise, other cleavage products, including N-terminally extended Aß (Welzel et al., 2014) and a similar peptide but with a truncated Aß C-terminus (Willem et al., 2015), were found to potently inhibit LTP *in vitro*. Currently it is uncertain how much these novel synaptotoxic APP metabolites, rather than Aß, contribute to synaptic disruption in AD.

The characterization of synaptotoxic Aß assemblies has been accompanied by complementary studies targeting Aß pharmacologically (Lee et al., 2017). One interesting recent advance is the finding that human antibodies that preferentially recognize Aß aggregates rather than monomers are effective against the inhibition of LTP by Aß-containing soluble AD brain extracts and may have therapeutic potential (Levites et al., 2015). This leads to the hope that presumably "physiological" monomers or other LTP-promoting APP metabolites (Ludewig and Korte, 2017) can be spared from being targeted in AD patients, which is likely to occur with secretase inhibitors or pan-Aß antibodies. Indeed, there is evidence that low concentrations of Aß perform a physiological role in maintaining certain forms of normal plasticity (Palmeri et al., 2017). While the poor ability of antibodies to cross the blood brain barrier may limit their clinical utility, certain brain penetrant small molecules can directly target synaptotoxic aggregate conformations shared between Aß and other amy-

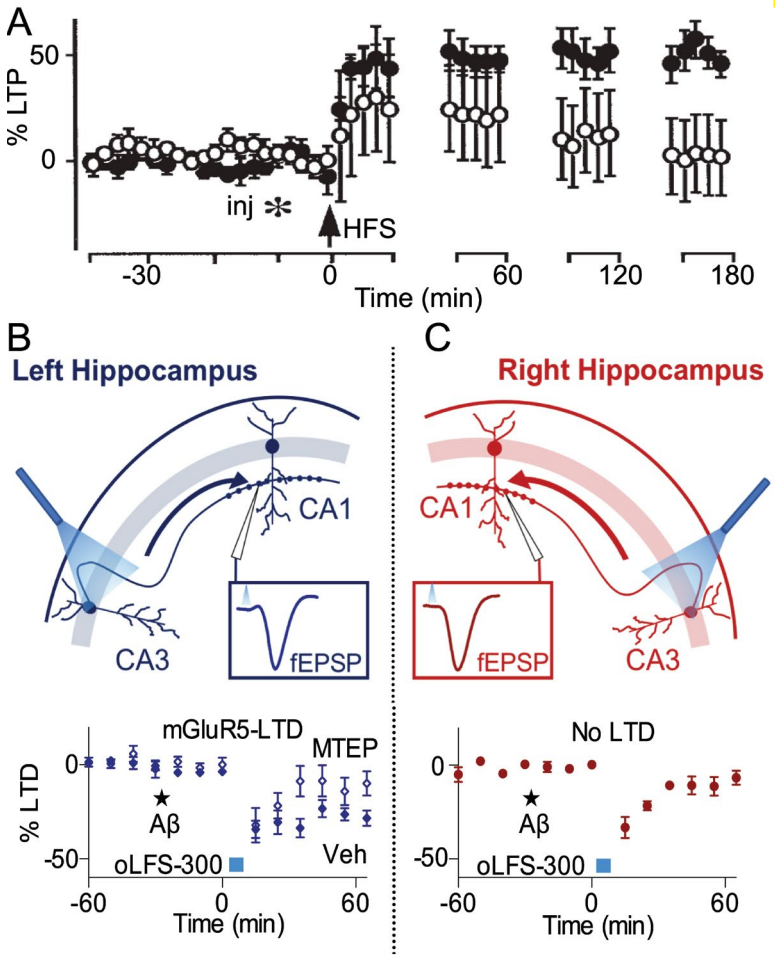

Fig. 1: Rapid, asymmetric synaptic plasticity disruption by amyloid-ß (Aß) *in vivo*.
A High frequency conditioning electrical stimulation (arrow, HFS) induced stable long-term potentiation (LTP) of hippocampal mixed pathway CA3-to CA1 synapses in vehicle-injected (closed circles; intracerebral, inj), anaesthetized rats. In contrast, the same HFS only induced a decaying LTP in animals injected with Aß1–42 (open circles). Modified from *Cullen et al., 1997 with permission*. **B, C** Aß preferentially facilitated the induction of long-term depression (LTD) at the CA3 input to CA1 pyramidal neurons of the left hippocampus. Selective optical stimulation (blue torch) of light-sensitive CA3 neurons in the left (**B**) or right (**C**) hippocampus. The light-sensitive Channel Rhodopsin 2 had been unilaterally transduced previously using an AAV viral vector injection into the CA3 area. Relatively weak, peri-threshold, low frequency conditioning optical pathway stimulation (oLFS-300, three hundred pulses at 1 Hz, blue bar), induced stable LTD of optically evoked field synaptic field potentials (fEPSP, insets) only in the left hippocampus of anaesthetized rats pre-injected with Aß. This LTD required metabotropic glutamate 5 receptor (mGluR5) activation, being blocked by the antagonist MTEP. Modified from *O'Riordan et al., 2018 with permission*. Values are mean±SEM.

loidogenic proteins including tau and α-synuclein. They can restore hippocampal LTP in an APP/PS1 mouse model even during an advanced stage of plaque formation (Martinez et al., 2018).

Given the inherent stickiness of misfolded aggregates of proteins such as $Aß_0$s, it is not surprising that they can bind to many physiologically important cellular sites. $Aß_0$s have been shown to bind to synapses in an activity- and NMDAR-dependent manner (Deshpande et al., 2009), but it is uncertain if intracellular or plasma membrane sites are the primary targets of synaptotoxic Aß, which is transported across membranes via a variety of carriers and also can form or link with ion channels within the membrane. Cellular prion protein, PrP, is perhaps the most established high affinity extracellular interacting protein for Aß oligomeric assemblies that inhibit LTP. In the presence of $Aß_0$s PrP apparently acts as a co-receptor with type 5 metabotropic glutamate receptor (mGluR5), triggering a cascade of intracellular events that alter signalling and NMDAR mechanisms that are mediated by the GluN2B-NMDAR subtype and regulate synaptic plasticity (Purro et al., 2018). Activation of GluN2B NMDARs in the presence of Aß also promotes another synaptotoxic pathway that includes the downstream effector JACOB and nuclear CREB and results in reduction of LTP and synapses (Ronicke et al., 2011). At a circuit level, Aß preferentially enhances LTD of transmission at left CA3-CA1 apical synapses, presumably because the expression of mGluR5 and GluN2B in certain hippocampal pathways is lateralized (O'Riordan K et al., 2018) (Figure 1B, C). This lateralization of the synaptotoxic actions of Aß potentially may contribute to the pattern of brain circuit failure as AD progresses insidiously (Minkova et al., 2017).

Interestingly, Wang et al. (2017) report that LTP deficits caused by the synaptic toxicity of soluble $Aß_0$s and their binding to synapses require the presence of APP, thus indicating that APP has a role in AD pathogenesis beyond the generation of Aß.

Protein Tau

Intracellular neurofibrillary tangles (NFTs) are the other cardinal feature of AD. They are composed of aggregated hyperphosphorylated tau protein, a major microtubule (MT) associated protein in neurons, promoting axonal MT assembly and regulating MT structure and axonal transport. Human tau occurs in six isoforms, which include three or four MT-binding repeat domains (3R or 4R), and different N-terminal inserts (0N-, 1N-, or 2N-Tau). Under physiological conditions, 3R and 4R isoforms are in an equimolar ratio, tau is unfolded, highly soluble and primarily found in neuronal axons. Interestingly, functional deficits that are caused by aggregation of tau and the formation of NFTs are reversible to a certain extent, as shown in AD tau mouse models in which the expression of a human tau transgene was switched off for different periods of time (Polydoro et al., 2013; Sydow et al., 2011). We examined such a recovery of synaptic function by measuring LTP in double-transgenic mice with regulatable expression of a human transgene (Tau_{RD}/ΔK280) that promotes tau aggregation by enhancing the propensity for ß-structure (pro-aggregant mice) (Figure 2A, B) (Sydow et al., 2011). Promotion of the ß-structure for 10 months resulted in a progressive pathology that led to the absence of LTP. Suppressing ß-structure and aggregation (anti-aggregant mice), in contrast, even increased LTP relative to wild-type mice. Switching off the transgene expression for 4 months brought the potentiation in all transgene groups back to normal levels. The recovery of LTP in pro-aggregant mice was paralleled by clearance of human tau from aggregates and its replacement by mouse tau as well as a 50 % recovery of the reduction in spine number caused by transgene expression [(Sydow et al., 2011); and unpublished data].

Although several post-translational tau modifications were found to be of pathological importance including acetylation and methylation, tau hyperphosphorylation remains a central pathophysiological trigger. Hyperphosphorylation leads to tau detachment from MTs and missorting into the somatodendritic compartment and further into synaptic spines. The latter precedes synapse loss and is sufficient to cause deficits in LTP by impairing glutamate receptor trafficking or synaptic anchoring (Polanco et al., 2018). Hyperphosphorylation of tau is caused by a disturbed balance between tau-kinases and tau-phosphatases. We studied the importance of this balance in 10–12-month-old THY-Tau22 mice, a transgenic tau strain carrying the FTD-causing tau point mutations G272V and P301S in the human 4-R tau under the control of the Thy1.2 promotor (Ahmed et al., 2015) (Figure 2C, D). In these studies, we found that LTD, not LTP, provided a sensitive indicator of deficits in synaptic function. Application of long trains of 2 Hz-stimulation, a protocol that generates equally robust LTD from young to very old non-transgenic mice (Ahmed et al., 2011), failed to induce LTD in the hippocampal CA1-region of Thy-Tau22 mice. This deficit was rescued by either applying an inhibitor of the major tau phosphorylating enzyme glycogen synthase kinase 3ß (GSK3ß) or by promoting the activation of the main tau dephosphorylating enzyme protein phosphatase 2A (PP2A) using sodium selenate (Figure 2C, D). The former effect is an apparent paradox because the same concentration of the GSK3ß inhibitor led, in agreement with earlier reports (Peineau et al., 2007), to a severe LTD deficit in non-transgenic control mice. The rescue of LTD in THY-Tau22 mice was achieved at an age where obvious signs of severe tauopathy and cognitive decline are present including prominent hyper- and abnormal phosphorylation of tau, strong somato-dendritic pathology and impaired memory (Schindowski et al., 2006; Van der Jeugd et al., 2011). These results support the conclusion that functional deficits, which are the result of alterations in phosphorylation homeostasis, can be normalized *in vitro* on a short time scale.

In addition to the processes mentioned above, hyperphosphorylated and aggregated tau can cause deficits in synaptic function by a number of other mechanisms. For instance, hyperphosphorylation of tau at certain residues causes a relocation of the axon initial segment which induces a more depolarized threshold for action potential initiation and reduces firing in hippocampal CA1 neurons. This, in turn can contribute to deficits in LTP induction (Hatch et al., 2017).

Tau – minion or partner of Aß?

The characteristic widespread tau pathology of AD defined by tau hyperphosphorylation, mislocalization and aggregation occurs several years after the appearance of amyloid plaques. This is concordant with the extended "amyloid cascade hypothesis" in which the accumulation of pathological forms of Aß not only precedes the development of widespread tau pathology, but also drives it via multiple pathways, leading to neuronal dysfunction and neurodegeneration (Bloom, 2014; Lane et al., 2018). Strong evidence for such functional links came from studies which showed that tau is required for Aß-mediated toxicity and synaptic plasticity disruption (Ittner et al., 2010; Roberson et al., 2007; Shipton et al., 2011). Whereas hippocampal

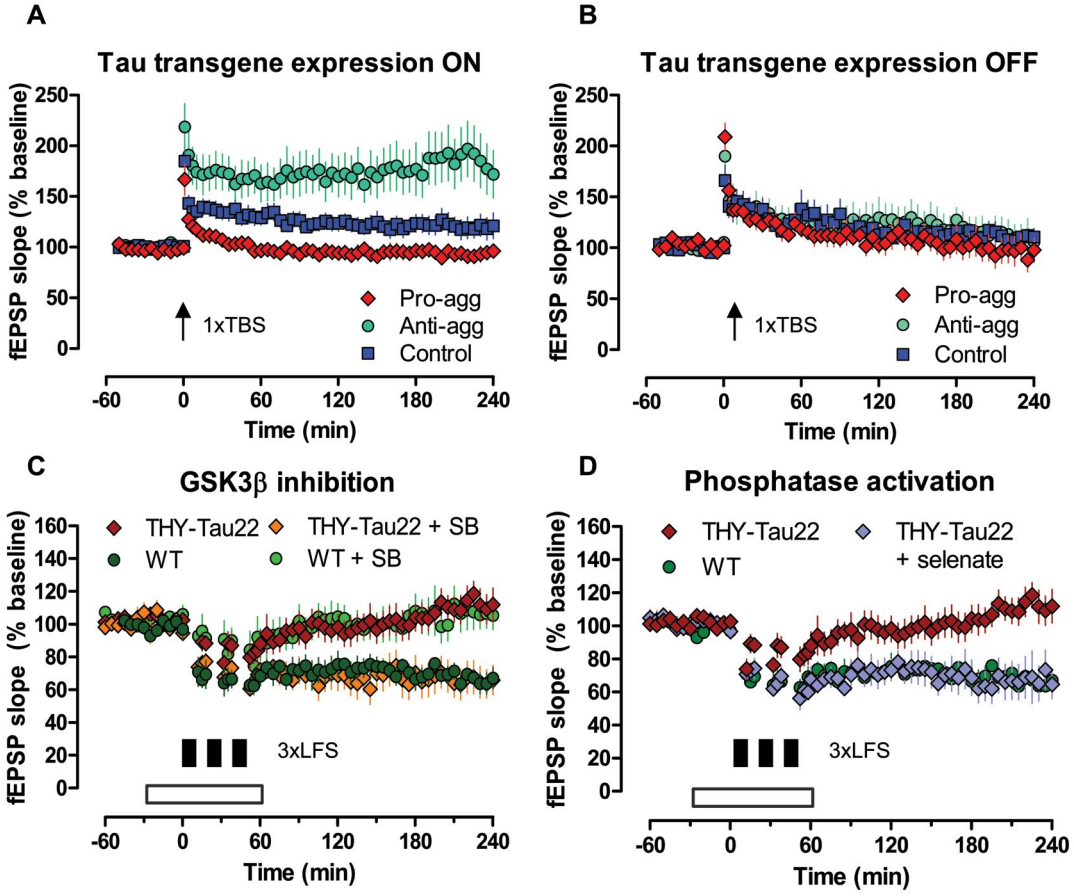

Fig. 2: Changes in tau conformation **(A,B)** and phosphorylation **(C,D)** result in accelerated pathology and functional decline that becomes overt as impaired LTP and LTD, respectively.
A Double-transgenic mice with regulatable expression of a human transgene (TauRD/ΔK280) that promotes tau aggregation failed to express LTP when the transgene was switched on for 10 months. Double transgenic mice that expressed a transgene that prevents aggregation (anti-aggregant mice) showed even a stronger LTP. *Modified from Sydow et al., 2011 with permission.* **B** Switching off the transgene expression for 4 months thereafter brought the potentiation in all transgene groups back to normal levels. Note that a weak form of LTP was induced by 1xTBS that is very sensitive to functional disturbances. **C** Inhibition of the tau phosphorylating enzyme GSK3ß by the selective inhibitor SB216763 reduces hyperphosphorylation and rescues impaired LTD in THY-Tau22 mice. Strikingly, LTD in WT mice was impaired by GSK3 inhibition. **D** Activation of tau dephosphorylating enzymes (here PP2A by sodium selenate) is an alternative way to reduce tau hyperphosphorylation and to rescue LTD in THY-Tau22 mice. This treatment had no effect on LTD in WT mice (data not shown). **C,D** *modified from Ahmed et al., 2015 with permission.*

LTP was severely impaired by Aß in control mice, the same treatment did not affect LTP in tau knockout mice. Moreover, blocking the Aß-induced increased phosphorylation of tau, using an inhibitor of GSK3, prevented the deleterious effect of Aß on LTP (Shipton et al., 2011). Thus, Aß-induced impairment of LTP requires the phosphorylation of tau.

Another example comes from research on the non-receptor tyrosine kinase Fyn, a component of the postsynaptic density (PSD) of excitatory synapses. Tau, in particular hyperphosphorylated tau, binds Fyn and delivers it to the PSD and more specifically to the GluN2B subunit of the NMDAR. Here Fyn regulates GluN2B-mediated NMDAR surface expression and NMDAR-dependent synaptic currents, both processes that are central to synaptic plasticity. These actions of Fyn are antagonized by the tyrosine phosphatase STEP (Boehm, 2013). In the presence of Aß, Fyn appears to exacerbate Aß's toxicity, by modulating NMDAR-dependent processes (Boehm, 2013).

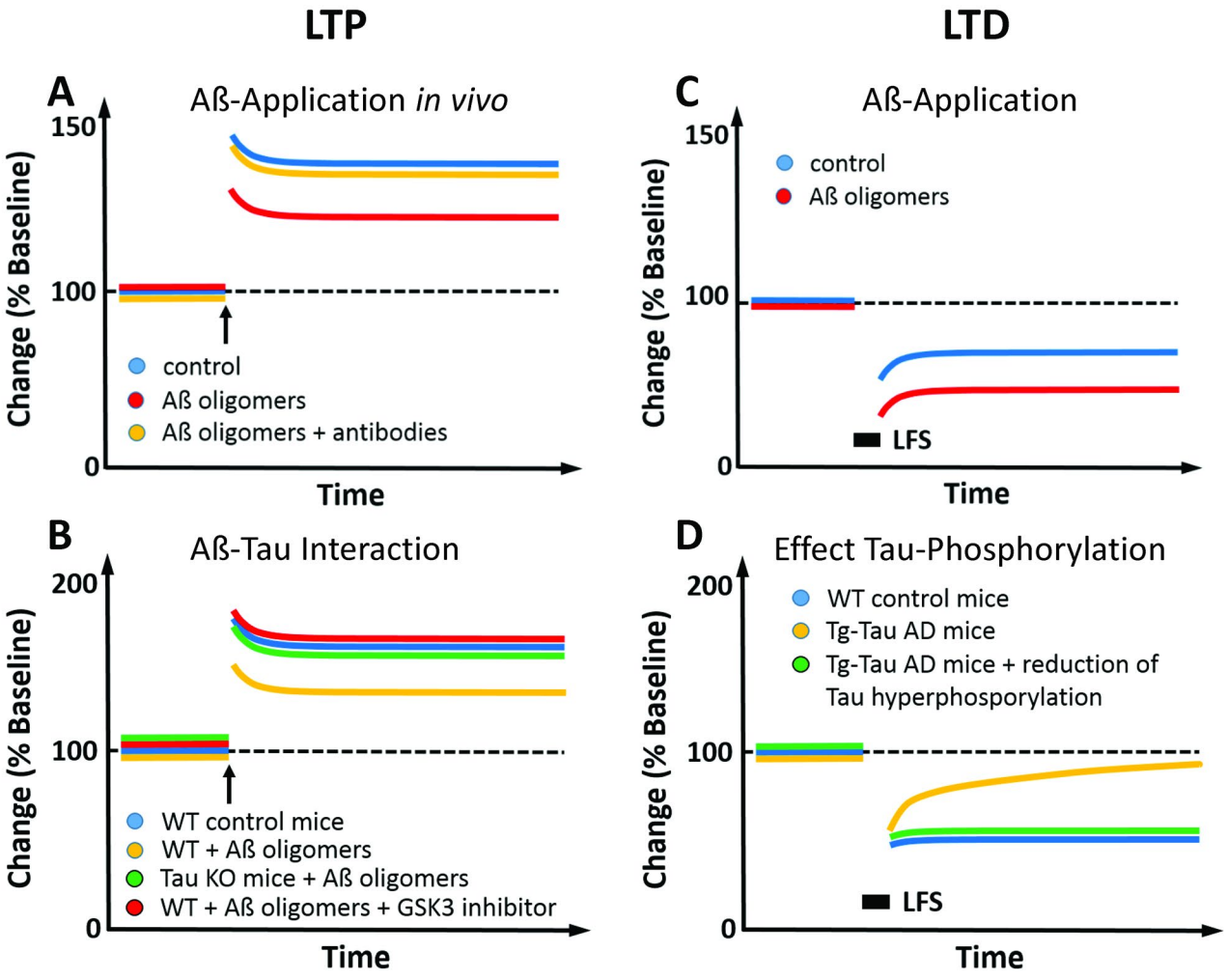

Fig. 3: Schematic diagrams exemplifying how specific pathological features of AD affect LTP and LTD, respectively. **(A, B)** Examples from LTP studies *in vivo* (**A**) and *in vitro* (**B**). **(C, D)** Examples from LTD studies *in vivo* (**C**) and *in vitro* (**C, D**). For details, see the papers cited. **A** Intraventricular infusion of Aß-fragments impairs LTP in the CA1-region *in vivo* (Cullen et al., 1997; Hu et al., 2018). **B** Protein Tau and hyperphosphorylation of Tau are required for the impairment of LTP by toxic Aß-fragments. Aß does not cause an LTP-deficit in Tau knock-out mice and in WT mice in which the hyperphosphorylation of Tau by Aß is prevented by an inhibitor of the major Tau-phosphorylating enzyme GSK3ß (Shipton et al., 2011). **C** Application of Aß-oligomers enhances LTD *in vivo* (Kim et al., 2001) and *in vitro* (Li et al., 2009). **D** Reducing Tau hyperphosphorylation by either inhibition of the tau phosphorylating enzyme GSK3ß or by promoting the activation of tau dephosphorylating enzymes (e. g. PP2A by sodium selenate) rescues impaired LTD in a Tg-Tau AD mouse model (Ahmed et al., 2015).

Progression of AD pathology by transcellular spreading of Aß and tau

Recent research has established that aggregates of Aß and tau are capable of transcellular propagation via synaptic and non-synaptic pathways thereby seeding Aß and tau pathology, respectively, in recipient neurons in a prion-like fashion (Eisele and Duyckaerts, 2016; Mudher et al., 2017). For example, the propagation of tau along neuronal circuits was reported to cause pathological tau transformations in the recipient region that lead to LTP deficits (Stancu et al., 2015)

Interestingly, there is evidence that amino-terminally truncated, pyroglutamylated (pE) forms of Aß including Aß3(pE)–42 cause tau-dependent neuronal death and template-induced misfolding of Aß42 into structurally distinct low-n oligomers that propagate by a prion-like mechanism (Nussbaum et al., 2012). Pyroglutamylated Aß 3(pE)-42 induces synaptic dysfunction to a similar extent as Aß42 but by clearly different mechanisms which are NMDAR independent, but mediated by the glial release of the proinflammatory cytokines (Grochowska et al., 2017).

Conclusion

Misfolded aggregation-prone Aß and tau drive cellular stress pathways that are also engaged by behavioural and inflammatory instigators of synaptic plasticity disruption shared with other brain diseases that may be comorbid with or precede AD. In AD, LTP and LTD have proven their sensitivity (i) to detect early presymptomatic deficits in synaptic function, (ii) to delineate the underlying mechanisms and (iii) to validate treatment strategies targeting synaptic proteins and circuits as the major locus of AD pathophysiology.

Acknowledgement: The authors thank David Blum (Univ. Lille, Inserm, CHU Lille, France), Klaus Reymann (LIN Magdeburg, Germany) and An Schreurs (KU Leuven) for critical suggestions. D. B. has been supported by FWO-Vlaanderen (grants G.0327.08 and G.0D76.14), MJR by Science Foundation Ireland (14/IA/2571) and the Irish Health Research Board (HRA-POR-2015-1102).

Glossary

AD	Alzheimer's disease
Aß	Amyloid ß
AMPAR	α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors
APOE4	Apolipoprotein E4
CA1	Cornu ammonis, subregion of the hippocampal formation
CREB	"cAMP response element-binding protein", cellular transcription factor
fAD	early familial (inherited) form of AD
KO	Knock-out
loAD	"late onset AD" – spontaneous form of AD with clinical symptoms becoming overt at higher age
low-n AßOs	Aβ oligomers resulting from the aggregation of two or several Aβ molecules
LTP	Long-term potentiation
LTD	Long-term depression
NMDAR	N-methyl-D-aspartate receptor
fEPSP	Excitatory postsynaptic field-potential
FYN	A Non-receptor tyrosine-protein kinase
JACOB	A neuronal protein
FTD	Frontotemporal Dementia
GSK3ß	Glycogen synthase kinase 3ß
HFS	brief high-frequency stimulation to induce LTP (typically 50–200Hz for 1s)
i.c.v.	intracerebroventricular; e. g. application of compounds directly into the ventricle
LFS	low-frequency stimulation to induce LTD (commonly 1–3 Hz for 5–15 min)
mGluRs	Metabotropic glutamate receptors
MT	Microtubule
NFT	Neurofibrillary tangles
PP2A	Protein phosphatase 2A
PSD	Postsynaptic density
PSEN1	Presenilin 1
PSEN3	Presenilin 2
PrP	Prion-Protein
STEP	A Tyrosine phosphatase
Tau	Protein Tau
WT	Wild type

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Article note: German version available at https://doi.org/10.1515/nf-2017-0063

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