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Inhibiting tumor necrosis factor-α before amyloidosis prevents synaptic deficits in an Alzheimer's disease model

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ABSTRACT

Deficits in synaptic structure and function are likely to underlie cognitive impairments in Alzheimer's disease. While synaptic deficits are commonly found in animal models of amyloidosis, it is unclear how amyloid pathology may impair synaptic functions. In some amyloid mouse models of Alzheimer's disease, however, synaptic deficits are preceded by hyperexcitability of glutamate synapses. In the amyloid transgenic mouse model TgCRND8, we therefore investigated whether early enhancement of glutamatergic transmission was responsible for development of later synaptic deficits. Hippocampi from 1-month-old TgCRND8 mice revealed increased basal transmission and plasticity of glutamate synapses that was related to increased levels of tumor necrosis factor α (TNFα). Treating these 1-month-old mice for 4 weeks with the TNFα inhibitor XPro1595 prevented synaptic deficits otherwise apparent at the age of 6 months. In this mouse model at least, reversing the hyperexcitability of glutamate synapses via TNFα blockade before the onset of amyloid plaque formation prevented later synaptic deficits.

1. Introduction

Synaptic loss is the best correlate of cognitive decline in Alzheimer's disease (AD) (Terry et al., 1991). It is commonly shown that synaptic function becomes impaired and decreased at later stages of amyloid pathology (Chapman et al., 1999; Nalbantoglu et al., 1997). Interestingly, an increase in neuronal activity is observed at early stages of pathology in various forms, such as in amyloid mouse models that exhibit increased susceptibility to seizures (Del Vecchio et al., 2004; Minkeviciene et al., 2009) and hyperexcitability of neuronal networks (Jolas et al., 2002; Palop et al., 2007; Verret et al., 2012). This increase in activity has also been documented in individuals with mild cognitive impairment (MCI) (Dickerson et al., 2005), *APOE ε4*-positive individuals (Bookheimer et al., 2000), and even in teenagers and young adults carrying an autosomal-dominant AD gene (Reiman et al., 2012). Furthermore, this paradoxical increase in activity has been postulated to precipitate the eventual decline in synaptic and cognitive function.

This early onset and temporal enhancement in glutamate synaptic function could be related to the proinflammatory cytokine tumor necrosis factor α (TNFα). Although TNFα is present at high levels in brains of AD patients postmortem (Grammas and Ovase, 2001) and in the peripheral circulation (Fillit et al., 1991), high levels of this cytokine are detectable even at early stages in both AD patients (Buchhave et al., 2010) and animal models (Cavanagh et al., 2013; Ferretti et al., 2012; Wright et al., 2013). The early appearance of this cytokine suggests that TNFα may be an upstream factor contributing to the development of AD pathology. Because AD develops over decades and the advanced stages are difficult to reverse, identification of early targets may lead to preventive approaches.

A prevalent view of the impact of TNFα on the pathogenesis of AD is that it exacerbates amyloid pathology. Indeed, TNFα can stimulate γ-secretase cleavage of amyloid precursor protein (APP)

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and expression of β-secretase to increase amyloid β (Aβ) production (Yamamoto et al., 2007). TNFα inhibition has therefore been examined in various transgenic AD models for its capacities to improve amyloid pathology (Gabbita et al., 2012; He et al., 2007; McAlpine et al., 2009; Tweedie et al., 2012). TNFα also modulates synaptic function, however (Santello and Volterra, 2012; Yirmiya and Goshen, 2011), and this effect of TNFα has not been studied in the context of AD, especially at early stages before amyloid plaque formation.

TNFα increases the surface expression of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) subtype of glutamate receptors (Stellwagen et al., 2005). TNFα also affects neuronal network development in the visual cortex (Kaneko et al., 2008) and the formation of long-term potentiation (LTP) (Tancredi et al., 1992). Using TgCRND8 mice that express both Swedish and Indiana mutations of APP (Chishti et al., 2001), we have shown that TNFα levels are increased in the hippocampus (Cavanagh et al., 2013) at least 1 month before amyloid plaque formation (Supplementary Fig. 1). This early onset increase in TNFα may increase glutamatergic transmission and overall excitability of neural networks in TgCRND8 mice.

2. Material and methods

2.1. Materials

Unless stated otherwise, all materials were purchased from Sigma Aldrich (St. Louis, MO, USA).

2.2. Mice

TgCRND8 mice that express both Swedish and Indiana mutations of APP (Chishti et al., 2001) and nontransgenic (NTG) control littermates were used. Experiments were carried out on both male and female 1-month-old and 6-month-old mice. TgCRND8 mice were studied at the age of 1 month because it has previously been shown that TNFα levels in the hippocampus are significantly increased at this time point (Cavanagh et al., 2013), and this finding was also confirmed in the present study (Supplementary Fig. 1). In addition, 1-month-old TgCRND8 mice are at least 1 month before amyloid plaque formation (Supplementary Fig. 1) (Goutagny et al., 2013). The advanced stage of 6 months was chosen because synaptic plasticity deficits have been described in TgCRND8 mice at this age and onward (Kimura et al., 2012). All experiments were performed on independent cohorts of mice except a subset of mice used in the inhibitory avoidance task that were then trained in the open field. Mice were housed in a 12-hour light and/or dark cycle (lights on: 8:00 AM) and had ad libitum access to food and water. All procedures were performed according to guidelines approved by the Canadian Council on Animal Care. As previously reported (Chishti et al., 2001), the mortality rate of TgCRND8 mice by 6 months was high (>50%). Interestingly, none of the XPro1595-treated NTG or TgCRND8 mice treated died by this age.

2.3. Immunohistochemistry

Mice were anesthetized by pentobarbital and transcardially perfused with phosphate-buffered saline (PBS) followed by 4% paraformaldehyde in PBS. Brains were postfixed overnight in the same solution, rinsed, and cryoprotected in 10% sucrose over 48 hours. Brain sections (50 μm) containing the dorsal hippocampal CA1 region were pretreated with formic acid ([90%], for 5 minutes, at room temperature [RT]). After 3–4 washes with PBS between each step of staining, the sections were incubated (for 1 hour, at RT) with PBS containing 1% normal goat serum, 0.25% Triton X-100, and 0.45% gelatin followed by overnight incubation with rabbit anti-FCA3340 to label $A\beta_{40}$ (Millipore, Canada; 1:1000; 4 °C). This antibody was chosen because it does not recognize APP or other APP-related C-terminal cleavage products. Sections were then incubated with Alexa 555-conjugated goat anti-rabbit IgG (Invitrogen, Carlsbad, CA, USA; 1:2000, for 2 hours, at RT). After nuclear labeling by 4′,6-diamidino-2-phenylindole (DAPI) (1:10,000, for 15 minutes, at RT), sections were washed and mounted on glass slides with Fluoromount-G (SouthernBiotech, Birmingham, AL, USA).

2.4. Enzyme-linked immunosorbent assay

Endogenous TNFα, an enzyme-linked immunosorbent assay (ELISA) directed at mouse TNFα (Biosensis, Temecula, CA, USA) was performed as previously described (Cavanagh et al., 2013). XPro1595, at 24 hours after subcutaneous injection of either 10-mg/kg XPro1595 or saline, mice were anesthetized and transcardially perfused with 0.9% saline to remove the blood in the brain. Dissected hippocampi were snap frozen on dry ice and stored at −80 °C until proteins were extracted in radioimmunoprecipitation assay (RIPA) buffer. Since XPro1595 is a mutated version of human TNFα, an ELISA kit directed at human TNFα (Biosensis) was used per the manufacturer's instructions to assess XPro1595 levels in TgCRND8-hippocampal RIPA extracts (Cavanagh et al., 2013). Protein concentrations were determined using the bicinchoninic assay kit (ThermoFisher, Canada).

2.5. Electrophysiology

Naïve mice were used in all electrophysiology experiments, with the exception of the 6-month-old mice that had received the pump implant. Slices were prepared as previously published (Tse et al., 2011). Mice were anesthetized using isoflurane, and brains were rapidly removed after decapitation. Coronal brain slices (350-μm thick) were cut in hyperosmotic, ice-cold, and carbogenated (5% CO_2, 95% O_2) slice-cutting solution (in mM: 252 sucrose, 2.5 KCl, 4 $MgCl_2$, 0.1 $CaCl_2$, 1.25 KH_2PO_4, 26 $NaHCO_3$, and 10 glucose; 360 mOsmol/L) using a vibratome. Freshly cut slices were incubated with carbogenated artificial cerebrospinal fluid (aCSF in mM: 125 NaCl, 2.5 KCl, 1 $MgCl_2$, 2 $CaCl_2$, 1.25 NaH_2PO_4, 26 $NaHCO_3$, and 25 glucose; 310 mOsmol/L) at 32 °C for 1 hour and subsequently maintained at RT. All postsynaptic responses were evoked by stimulating the Schaffer collateral-commissural pathway (constant current pulses [0.08 ms] through a tungsten-bipolar electrode [FHC, Bowdoin, ME, USA]) and recorded in the dorsal hippocampal CA1 stratum radiatum. Evoked field excitatory postsynaptic potentials (fEPSPs) were detected by aCSF-filled glass electrodes (WPI, Sarasota, FL, USA). All recordings were performed at RT.

2.5.1. Input output

fEPSPs were recorded in the presence of 5-μM bicuculline while incrementally increasing the fiber volley, which represents activation of presynaptic fibers, by 0.05 mV from 0 to 0.20 mV.

2.5.2. Long-term potentiation

After a stable recording of fEPSPs (20 minutes), LTP was induced via 10 stimuli at 100 Hz, 30 minutes later followed by a train of 4 bursts of 10 stimuli at 100 Hz every 20 seconds.

2.5.3. Drug treatment

XPro1595 was obtained by way of a Material Transfer Agreement with David E. Szymkowski from Xencor (Monrovia, CA, USA). Slices were treated with vehicle (aCSF) or XPro1595 (100 ng/mL) for at least 1 hour prior to recording. XPro1595-treated slices were

subsequently perfused with the same concentration of XPro1595 throughout the recording.

2.6. Behavior

2.6.1. Inhibitory avoidance

A plexiglass box with 2 compartments (light and dark) separated by a trap door was used. Training: mice were placed in the lighted, safe compartment. The trap door was opened after 10 seconds, and the animal was allowed to step through at will. The trap door was then closed and the mouse received a 1-second 0.5-mA scrambled foot shock via electrified steel rods on the floor. The mouse was removed immediately after the shock. Mice spending longer than 5 minutes in the light side of the chamber on the day of training were discarded. Retention: it was performed 24 hours later (day 2) and then again 1-week post training (day 8) by placing trained mice back in the lighted compartment and measuring latencies for the animals to re-enter the dark compartment. No shock was given during retention trials. The retention trials were ended if the mice did not cross to the dark compartment after 7 minutes. Genotypes of mice were unknown to the experimenters. Drug treatment: a 10-mg/kg XPro1595 or saline subcutaneous injection was given 24 hours before training to allow enough time for the drug to pass through the blood–brain barrier and reduce stress caused by injection, which may affect the animals' performance.

2.6.2. Open field

One day after the 1-week retention trial, a subset of mice from each group were subcutaneously injected with either 10-mg/kg XPro1595 or saline, as before. The next day, mice were allowed to explore a 60 cm × 60 cm plexiglass open field (divided into 16 equal squares with the 4 center squares defined as the "center") for 5 minutes. The TopScan Behavior Analyzing System (Clever Sys Inc, Reston, VA, USA) was used to track each animal's movements.

2.6.3. Fear extinction

Mice were trained in the inhibitory avoidance apparatus as described so that they all received a foot shock after they crossed to the dark chamber. Extinction trials without shock were performed 24 hours, 3, 5, and 7 days later, each with a 1-minute "extinction" period after crossing to the dark chamber where the mouse was kept in the dark compartment to lessen the association between this compartment and the shock.

2.7. Osmotic pump implants

One-month-old TgCRND8 mice and NTG controls were anesthetized with isoflurane throughout the procedure. Mice were implanted subcutaneously with an Alzet osmotic (Cupertino, CA, USA) pump model #1004 containing 10 mg/kg/day of XPro1595 or a saline solution. The pumps were removed 4 weeks later. The animals were assessed only when they reached 6 months of age. In order to rule out any effects of the pump implant surgery, the input and/or output function of saline-treated mice (both NTG and TgCRND8) was compared to that of untreated controls from the same genotype at 6 months. No significant differences in input and output were found between pump-implanted and untreated mice of either of the genotypes (data not shown).

2.8. Data analysis

All data were tested for normality using the Shapiro–Wilks test, and the appropriate parametric or nonparametric test was subsequently used for analysis. All data are represented as mean ± standard error of the mean.

3. Results

3.1. Preplaque 1-month-old TgCRND8 mice displayed TNFα-dependent increase in excitatory synaptic function and LTP

Input–output curves of evoked fEPSPs in the hippocampal CA1 region were compared between slices from 1-month-old TgCRND8 mice and NTG littermates. A repeated measures group by fiber volley size analysis of variance (ANOVA) revealed a significant interaction ($F_{(12, 224)} = 10.6$, $p < 0.001$). The ANOVA was decomposed by Tukey's post hoc comparisons that revealed significant differences at fiber volley sizes 0.10, 0.15, and 0.20 mV. The fEPSP slopes recorded from TgCRND8 mice were significantly greater than those from NTG mice, under control conditions between fiber volley sizes 0.15 and 0.20 mV ($p < 0.05$). To examine the contribution of TNFα to enhanced synaptic function in preplaque TgCRND8 mice, we studied the effect of the dominant-negative soluble TNFα inhibitor, XPro1595, on synaptic function. In hippocampal slices from TgCRND8 mice, the slope of fEPSPs was significantly greater in control slices compared to XPro1595-treated for fiber volley sizes 0.10–0.20 mV ($p < 0.05$). No significant drug effects were observed in slices from NTG mice (Fig. 1A). We also observed a significantly greater percent decrease in mean fEPSP slope caused by XPro1595 treatment in slices from TgCRND8 mice (48.10 ± 1.46%) compared to slices from NTG mice (38.89 ± 1.44%, $t_{(18)} = 4.50$, $p < 0.001$). No significant differences between NTG and TgCRND8 mice were detected in miniature excitatory postsynaptic currents, paired pulse ratio, or N-methyl-D-aspartate (NMDA)/AMPA ratio (data not shown).

This increase in input–output function could facilitate hippocampal LTP in TgCRND8 mice. We tested this prediction with a stimulating protocol that was previously used to show enhanced LTP in 9-week-old TgCRND8 mice (Jolas et al., 2002) and comparing potentiation in vehicle- or XPro1595-treated acute hippocampal slices from 1-month-old TgCRND8 and NTG mice (Fig. 1B). A 2-factor, between-subjects ANOVA revealed a significant drug by genotype interaction ($F_{(1,42)} = 5.25$, $p < 0.05$). Simple effects tests indicated that the percent potentiation of the fEPSP slope in the last 5 minutes of recording was greater in slices from TgCRND8 mice compared to NTG under vehicle conditions ($p < 0.05$), indicating that TgCRND8 mice showed increased LTP. Furthermore, while XPro1595 treatment had no effect in slices from NTG mice, it significantly ($p < 0.01$) abolished the increased LTP in slices from TgCRND8 mice.

3.2. Preplaque 1-month-old TgCRND8 mice displayed TNFα-dependent enhancement in hippocampal cognitive function

Next, we used a hippocampus-dependent inhibitory avoidance task to determine whether the facilitation of hippocampal synaptic function and LTP is translated into enhanced cognitive function at this preplaque stage. To ensure that XPro1595 can cross the blood–brain barrier, we compared hippocampal levels of XPro1595 in TgCRND8 and NTG mice that were subcutaneously injected 24 hours earlier with either 10-mg/kg XPro1595 or saline. Using a 1-factor, between-subjects ANOVA $F_{(2,12)} = 28.80$, $p < 0.001$ followed by Tukey's post hoc test, we found a significantly higher level of XPro1595 ($p < 0.001$) in hippocampal tissue of drug-injected mice than in saline-injected for both NTG and TgCRND8 (Fig. 2A). Importantly, no difference was found in hippocampal XPro1595 levels between NTG and TgCRND8 mice, suggesting no differences in hippocampal delivery of this drug from systemic administration between these mice.

We compared the performance of saline- or XPro1595-treated 1-month-old TgCRND8 and NTG mice in the inhibitory avoidance test (Fig. 2B). On the training day (day 1), while there was no significant difference in the mean latency to enter the dark chamber

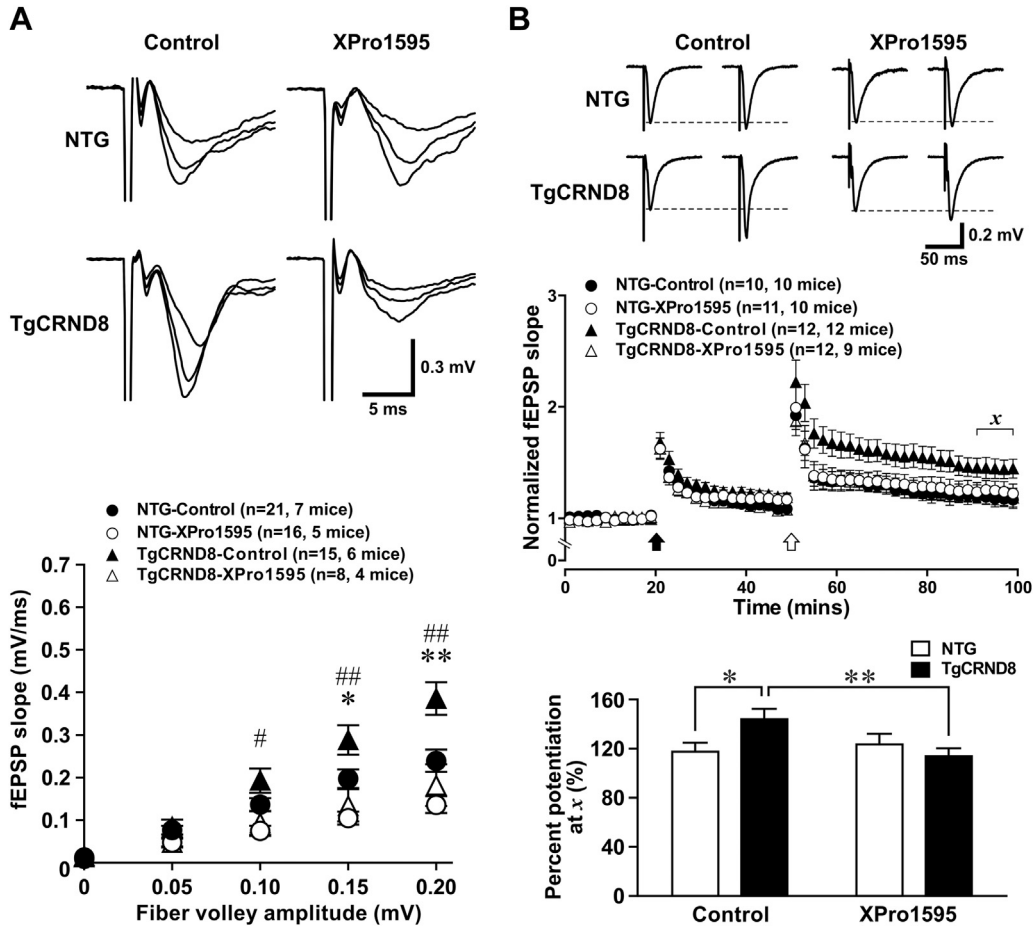

Fig. 1. Increase in synaptic function and plasticity is TNFα dependent. (A) Upper: representative fEPSP traces. Lower: slope of evoked fEPSP represented as a function of fiber volley amplitude. The fEPSP slopes recorded from TgCRND8 mice were significantly greater than those from NTG mice, under control conditions. In hippocampal slices from TgCRND8 mice the slope of fEPSPs was also significantly greater in control slices compared to XPro1595-treated for fiber volley sizes 0.10–0.20 mV. (NTG vs. TgCRND8: $^{*}p < 0.05$, $^{**}p < 0.01$; control vs. XPro1595-treated: $\#p < 0.05$, $\#\#p < 0.01$). (B) Upper: representative fEPSP traces under baseline (left) and in the last 5 minutes of recording (right). Middle: scatter plots show normalized fEPSPs over the course of the recording. The black arrow represents induction of 10 stimuli at 100 Hz and the white arrow represents train of 4 bursts of 10 stimuli at 100 Hz. Note the enhanced LTP in the TgCRND8 group under control conditions. Lower panel: bars represent percent potentiation over the last 5 minutes of the recording. Slices from TgCRND8 mice under control conditions were significantly potentiated compared to slices from NTG mice under control conditions and slices from TgCRND8 mice treated with XPro1595 ($^{*}p < 0.05$ and $^{**}p < 0.01$). Abbreviations: fEPSP, field excitatory postsynaptic potential; LTP, long-term potentiation; NTG, nontransgenic; TNFα, tumor necrosis factor α.

between NTG and TgCRND8 mice, a 2-factor ANOVA revealed a significant drug treatment effect ($F_{(1,92)} = 15.02$, $p < 0.001$), indicating an increase in latency in all XPro1595-treated mice. Despite seeing this drug effect on the training day, we saw no effect of XPro1595 in any of the groups on the 24-hour retention trial (day 2). When retention was tested again the following week (day 8), a Kruskal–Wallis followed by Mann–Whitney tests revealed a significant difference between the groups ($H_{(3)} = 8.26$, $p < 0.05$), where TgCRND8 mice displayed a significantly longer latency to enter the dark chamber than NTG mice ($p < 0.05$). Furthermore, TgCRND8 mice treated with XPro1595 had a significantly lower latency than untreated TgCRND8 mice ($p < 0.05$), suggesting that blocking TNFα signaling was sufficient to abolish the enhanced performance of TgCRND8 mice on the 1-week retention.

3.3. Enhanced performance of TgCRND8 mice in the inhibitory avoidance is not related to changes in motility, anxiety, or a deficit in extinction learning

Apart from enhanced cognitive function, the increase in latency on the inhibitory avoidance task could also be due to decreased motility or enhanced anxiety-related behavior in TgCRND8 mice. However, using the open-field task, we found that TgCRND8 mice traveled a significantly greater total distance in the open field and thus were more active than NTG mice (a 2-factor, between-subjects ANOVA, genotype effect: $F_{(1,43)} = 6.01$, $p < 0.05$). In addition, TgCRND8 mice spent more time in the center than NTG mice regardless of their treatment group as revealed by a 2-factor, between-subjects ANOVA (genotype effect: $F_{(1,43)} = 4.85$, $p < 0.05$). Interestingly, XPro1595 may have an anxiogenic effect, since drug treatment in either genotype led to a decrease in time spent in the center (drug effect: $F_{(1,43)} = 5.11$, $p < 0.05$, Fig. 3A). Finally, since the retention test of day 2 could serve as extinction training by lessening the association between the dark compartment and the shock on the training day (day 1), another possibility is that the TgCRND8 mice may have impairments in fear extinction. However, when we compared extinction of fear memory between these 2 groups after multiple extinction trials (1, 3, 5, and 7 days post training), no significant differences in retention latencies were found between genotypes (Fig. 3B).

3.4. Early inhibition of TNFα signaling produces lasting effects on baseline synaptic function

We then set out to determine whether attenuating this early TNFα-dependent increase in synaptic function could produce

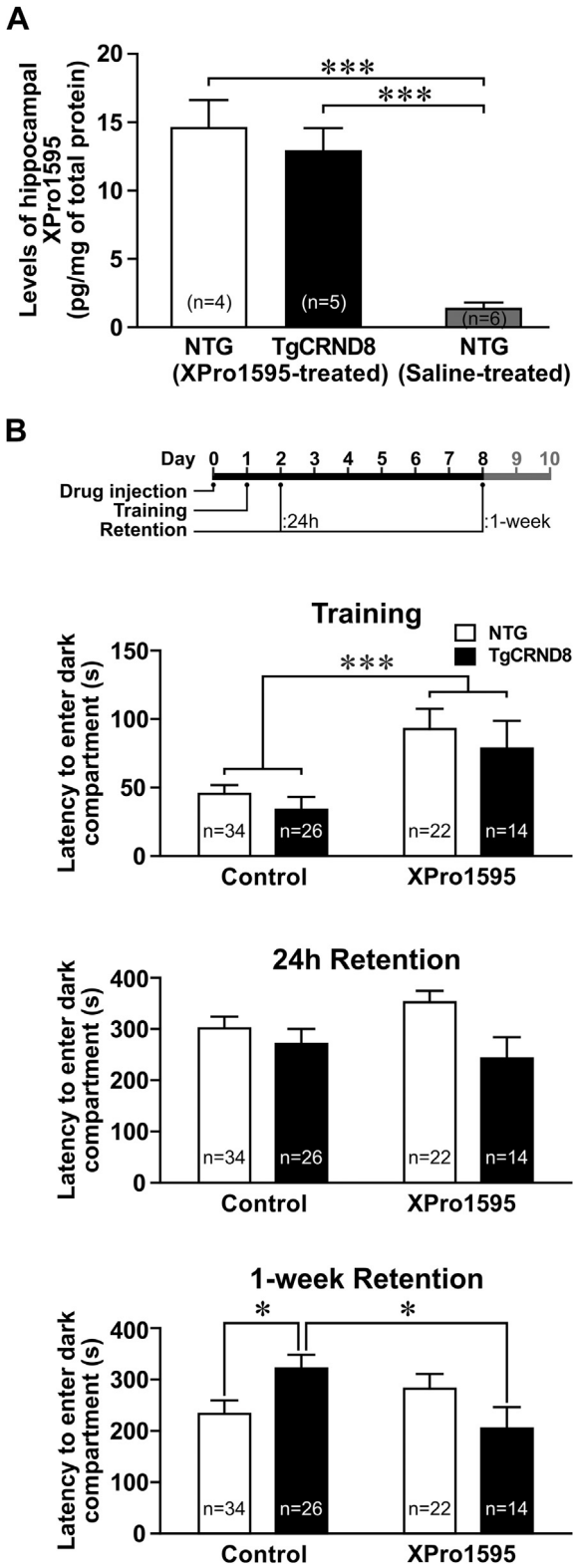

Fig. 2. Improved performance on inhibitory avoidance task is TNFα dependent. (A) Hippocampal XPro1595 is significantly higher in both genotypes compared to saline-injected mice (***$p < 0.001$). (B) Schematic representation of drug injection and testing schedule. Bar graphs represent latencies to enter dark compartment on training day, 24-hour retention trial, and 1-week retention trial, respectively. A significant drug treatment effect was detected on the training day (day 1), yet no differences were detected in latencies on the 24-hour retention trial (day 2). On the 1-week retention trial (day 8), a significant increase in latency was measured in TgCRND8 mice compared to NTG mice, whereas TgCRND8 mice treated with XPro1595 had latencies that were significantly lower than untreated TgCRND8 mice (*$p < 0.05$). Abbreviations: NTG, nontransgenic; TNFα, tumor necrosis factor α.

lasting effects on synaptic pathology at a later time point (6 months). Chronic 4-week-long XPro1595 treatment from 1 to 2 months was administered through a subcutaneously implanted osmotic pump. At 6 months, mice were sacrificed for electrophysiological assessment of hippocampal synaptic function and plasticity. When comparing input-output curves, a repeated measures group by fiber volley size ANOVA revealed a significant interaction ($F_{(12,\ 332)} = 8.69$, $p < 0.001$). The ANOVA was decomposed by Tukey's post hoc comparisons that revealed significant differences at fiber volley sizes 0.10, 0.15, and 0.20 mV. Compared to 1-month-old mice, we observed the opposite phenomena in hippocampal slices from these older, 6-month-old TgCRND8 mice, such that the slope of fEPSPs were significantly lower in slices from TgCRND8 mice compared to NTG mice for fiber volley sizes 0.10–0.20 mV ($p < 0.05$, Fig. 4A). Remarkably, the input-output function in 6-month-old TgCRND8 mice that received XPro1595 treatment at a prodromal age was significantly higher than saline-treated TgCRND8 mice ($p < 0.05$) for the same fiber volley sizes and not significantly different than NTG controls. No significant difference was observed in NTG saline- and NTG-XPro1595-treated mice. Furthermore, we did not see differences in LTP between any of the groups (Fig. 4B). Unfortunately, perhaps due to their C3H hybrid background (Sidman and Green, 1965; Wong and Brown, 2006), both TgCRND8 mice and NTG littermates exhibited visual impairments at 6 months so that we were unable to examine their performance in inhibitory avoidance.

4. Discussion

In this study, we show increased glutamatergic function and LTP in 1-month-old TgCRND8 mice, months before amyloid plaque formation (Chishti et al., 2001). TgCRND8 mice also exhibited enhanced hippocampal cognitive function in the inhibitory-avoidance task at the preplaque stage. These enhancements in hippocampal synaptic and cognitive functions could be reversed by inhibiting TNFα using the dominant-negative biologic, XPro1595. Furthermore, inhibiting TNFα in 1-month-old TgCRND8 mice for 4 weeks prevented deficits in synaptic function otherwise apparent at 6 months. To our knowledge, these data provide evidence for the first time that the preplaque increase in TNFα enhances hippocampal synaptic and cognitive function and precipitates later stage synaptic impairments in TgCRND8 mice.

In addition to its implicated immune function, the increased TNFα in 1-month-old TgCRND8 mice (Supplementary Fig. 1) could have collateral effects on enhancing baseline glutamatergic transmission in the hippocampus. Because TNFα increases the surface expression of calcium-permeable, GluA2-subunit-containing AMPA receptors (Ogoshi et al., 2005; Stellwagen et al., 2005), this cytokine has been linked to excitotoxicity (Leonoudakis et al., 2004) and the pathophysiology of seizures (Li et al., 2011). Accordingly, genetic deletion of TNFR1, the preferential binding site of soluble TNFα, can decrease excitatory synaptic transmission (He et al., 2012). This synaptic effect of TNFα may underlie the enhancement of glutamatergic transmission and LTP in 1-month-old TgCRND8 mice, since XPro1595 could reverse these enhancements (Fig. 1). Interestingly, similar to Jolas et al., (2002), we failed to observe a parallel increase in basal miniature synaptic function in TgCRND8 mice. These findings suggest that alterations at the network level could be responsible for the enhancement of excitatory synaptic transmission in these mice and have also been documented in 1-month-old TgCRND8 mice (Goutagny et al., 2013).

XPro1595 inhibits soluble TNFα signaling while sparing transmembrane TNFα signal transduction (McCoy and Tansey, 2008). XPro1595 works by forming inactive heterotrimers with soluble TNFα monomers, thereby sequestering the endogenous protein and

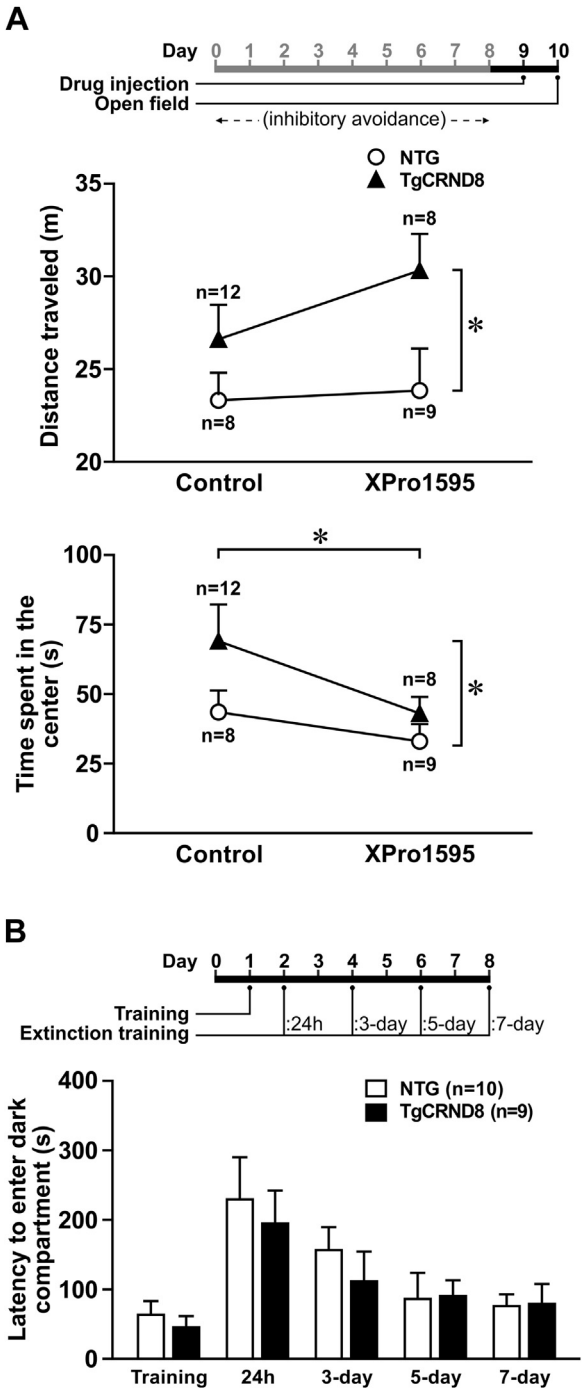

Fig. 3. Motility, anxiety, and extinction learning are not linked to inhibitory avoidance performance. (A) Schematic representation of drug injection and testing schedule. TgCRND8 mice travel a significantly greater distance in the open field. Analysis of the time spent in the center indicated that TgCRND8 mice spend more time in the center of an open field and XPro1595-treated mice of either genotype spend more time in the periphery ($^{*}p < 0.05$). (B) Schematic representation of drug injection and testing schedule. Histogram shows performances of mice in fear extinction trials, which are not significantly different between groups. Abbreviation: NTG, nontransgenic.

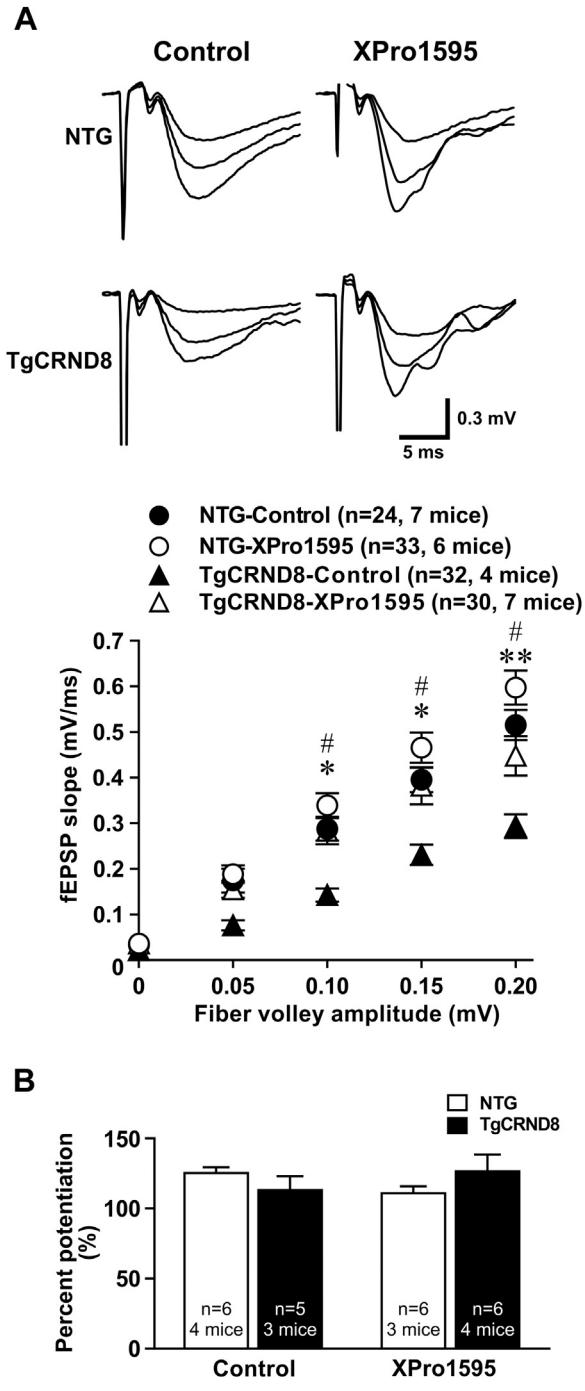

Fig. 4. Early TNFα inhibition prevents synaptic deficits in 6-month-old TgCRND8 mice. (A) Upper: representative fEPSP traces. Lower: slope of evoked fEPSP represented as a function of fiber volley amplitude. The fEPSP slopes recorded from TgCRND8 mice were significantly lower than those from NTG mice, under control conditions. The slope of fEPSPs in 6-month-old TgCRND8 mice was also significantly lower under control conditions compared to XPro1595-treated for fiber volley sizes 0.10–0.20 mV. (NTG vs. TgCRND8: $^{*}p < 0.05$, $^{**}p < 0.01$; control vs. XPro1595 treated: $\#p < 0.05$). (B) Bars represent percent potentiation over the last 5 minutes of the recording. No significant differences were detected between any of the groups. Abbreviations: fEPSP, field excitatory postsynaptic potential; NTG, nontransgenic, TNFα, tumor necrosis factor α.

preventing downstream signaling through the receptor. This mechanism of action is of therapeutic interest because the transmembrane form of TNFα is involved in innate immunity and defense against infection, whereas the soluble form of TNFα is involved in AMPA receptor insertion (Stellwagen et al., 2005) and cell death (McCoy and Tansey, 2008). Not surprisingly, XPro1595 has been found to be therapeutically beneficial in models of Parkinson's disease (Barnum et al., 2014), Huntington's disease (Hsiao et al., 2014), and multiple sclerosis (Yang et al., 2013). Using ELISA, we found that the XPro1595 biologic was present in perfused hippocampal tissue 24 hours after a single subcutaneous injection.

Peripheral injections of XPro1595 have been used in other studies that produced central effects (Barnum et al., 2014; Lewitus et al., 2014; Yang et al., 2013). Subcutaneous injections of 10-mg/kg XPro1595, the dosage used in the present study, could reduce microglial activation and rescue nigral–neuronal death caused by 6-hydroxydopamine (6-OHDA) in rats (Barnum et al., 2014). A 30-mg/kg intraperitoneal injection could also produce electrophysiologically measurable effects after 2 days in the striatum (Lewitus et al., 2014). Our ELISA data confirm the presence of XPro1595 in the hippocampus after a single subcutaneous injection during inhibitory avoidance training.

Our findings suggest that TgCRND8 mice displayed enhanced hippocampus-dependent memory formation at 1 month of age. First, we saw a facilitation of hippocampal LTP, which has been associated with memory formation in the inhibitory avoidance task by causing an increase in fEPSP slopes, which subsequently occluded LTP formation in vivo (Whitlock et al., 2006). Second, we found that TgCRND8 mice traveled a significantly greater distance in the open field compared to controls, which rules out any debilitating deficits in motility that would prevent the mice from being able to cross to the dark compartment on the inhibitory avoidance task. Notably, this increase in motility supports previous findings that several AD transgenic mouse models display increased locomotor function (Ambree et al., 2009; Ma and McLaurin, 2014). Third, in parallel with previous findings at a later age (Ma and McLaurin, 2014), we found that TgCRND8 mice spent a significantly greater amount of time in the center compared to controls, indicating that these mice displayed less anxiety-related behavior and suggesting that anxiety induced by the shock is not the cause of the animals' increased latency. Reduced anxiety has also been previously reported in TgCRND8 mice using the elevated plus maze after environmental enrichment (Gortz et al., 2008). Finally, we observed similar extinction learning between TgCRND8 and NTG mice. Taken together, with the increase in LTP, these behavioral findings suggest that TgCRND8 mice displayed enhanced hippocampus-dependent memory formation at 1 month of age. Similarly, Espana et al., (2010) found enhanced fear memory in the contextual fear conditioning task in the APP_{Ind}, $APP_{Swe/Ind}$, and 3xTgAD mouse models and suggested that these enhancements are related to increased consolidation. Nonetheless, the decline in performance of TgCRND8 mice on various behavioral tasks (Chishti et al., 2001), including the step-down passive avoidance task in 7-month-old animals (Bellucci et al., 2006), suggests that the enhancement of hippocampal synaptic and cognitive functions as shown in the inhibitory avoidance task is transient.

The TNFα-dependent increase in hippocampal synaptic and cognitive functions could have pathological outcomes. Indeed, increased activity has been detected in various forms in early stages of pathology in humans as well as mouse models. For instance, increased hippocampal activation has been detected by functional magnetic resonance imaging in patients with MCI (Dickerson et al., 2005) as well as in cognitively normal, older Aβ-positive individuals (Elman et al., 2014). Carriers of the *APOE ε4* allele, the main genetic risk factor for AD, have also shown greater activation while performing memory-activation tasks in brain regions affected in AD (Bookheimer et al., 2000). Findings from mouse models suggest that this increased synaptic function could precipitate hypersynchronous activity (Verret et al., 2012), seizures (Del Vecchio et al., 2004; Palop and Mucke, 2009), or excitotoxicity (Leonoudakis et al., 2008) later on. Our findings strongly suggest that the preplaque increase in TNFα could be responsible for enhancing brain excitability by increasing glutamate synaptic function. Notably, evidence from a mouse model of AD as well as in AD patients suggests that this hyperactivity may also be due to decreased γ-aminobutyric acid (GABA)ergic transmission (Verret et al., 2012) or GABAergic loss (Baglietto-Vargas et al., 2010; Krantic et al., 2012; Ramos et al., 2006; Takahashi et al., 2010). Incidentally, TNFα can cause endocytosis of GABA receptors and lead to a decrease in inhibitory synaptic function (Stellwagen et al., 2005). Whether this cytokine is involved in decreasing the strength of inhibitory synapses in AD-like models remains to be tested.

Findings from 6-month-old saline-treated TgCRND8 mice show that these mice had decreased glutamatergic function compared to saline-treated, age-matched controls (Fig. 4). These data are consistent with the idea that the early increase in synaptic plasticity is short lasting and dissipated with advancing amyloid pathology. The early increase in TNFα was targeted to study the possible long-term therapeutic effects of inhibiting TNFα and the associated increase in synaptic function. Remarkably, just 4 weeks of TNFα inhibition by XPro1595 at a preplaque age was enough to rescue the decrease in input-output function in 6-month-old mice. Similarly, normalizing proinflammatory cytokine production in 6-month-old APP/PS1 mice improved synaptic protein loss in 11-month-old mice; however, synaptic function was not assessed under this intervention paradigm (Bachstetter et al., 2012). Further experiments will be needed to assess whether inhibiting TNFα at a prodromal stage can rescue cognitive impairments at a later time point. Importantly, nonvisual behavioral tasks should be used since visual impairments are well documented in C3H strains (www.jax.org/strain/000659). These impairments may not have been previously reported since TgCRND8 mice are bred on a hybrid background, which may induce variability in data both within and across laboratories. Nonetheless, targeting hippocampal hyperactivity with the antiepileptic drug, levetiracetam, reduced cognitive impairments in patients with amnestic MCI (Bakker et al., 2012) and also reversed synaptic and cognitive deficits in a mouse model of the disease (Sanchez et al., 2012). Accordingly, normalizing excess neural activity through overexpression of the inhibitory neuropeptide Y 13–36 (Koh et al., 2010) as well as through positive allosteric modulation of the $GABA_A$ α5 receptor subunit (Koh et al., 2013) improved hippocampal-dependent memory in cognitively impaired aged rats. Treatment with levetiracetam or sodium valproate also dose dependently improved memory impairments in aged rats (Koh et al., 2010). Furthermore, modulating neuronal activity through a chemogenetic approach decreased Aβ aggregation and the loss of synaptic structures near plaques (Yuan and Grutzendler, 2016). To our knowledge, our study is the first to identify that increased TNFα may be the mechanism underlying enhanced glutamatergic transmission in TgCRND8 mice.

5. Conclusions

A wealth of literature suggests that neuroinflammation can be a "double-edged sword" (Aggarwal, 2003; Santello and Volterra, 2012; Wyss-Coray and Mucke, 2002) so that low-level inflammatory mediators that may be beneficial can become neurotoxic when chronically increased. Indeed, TNFα levels are likely chronically elevated, since they are high even in 7-month-old TgCRND8 mice (Cavanagh et al., 2013). Given the importance of synaptic pathology to cognitive deficits in AD, a chronic increase in TNFα starting at preplaque stages could precipitate the deleterious symptoms at later stages. Our findings in the early intervention paradigm suggest that inhibiting TNFα could be considered a prodromal treatment for correcting certain aspects of synaptic pathology in AD. Indeed, several studies have reported a reduced risk of AD when treating individuals with nonsteroidal anti-inflammatory drugs well before the onset of overt cognitive symptoms (Breitner et al., 2011; Hayden et al., 2007). Targeting TNFα may be a treatment for preventing synaptic deficits of AD.

Disclosure statement

The authors have no actual or potential conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version at http://dx.doi.org/10.1016/j.neurobiolaging.2016.07.009.

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