



NMDA receptors and BAX are essential for A β impairment of LTP

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Accumulation of amyloid- β (A β) is a hallmark of Alzheimer's disease, a neurodegenerative disorder in which synapse loss and dysfunction are early features. Acute exposure of hippocampal slices to A β leads to changes in synaptic plasticity, specifically reduced long-term potentiation (LTP) and enhanced long-term depression (LTD), with no change in basal synaptic transmission. We also report here that D-AP5, a non-selective NMDA receptor antagonist, completely prevented A β -mediated inhibition of LTP in area CA1 of the hippocampus. Ro25-6981, an antagonist selective for GluN2B (NR2B) NMDA receptors, only partially prevented this A β action, suggesting that GluN2A and GluN2B receptors may both contribute to A β suppression of LTP. The effect of A β on LTP was also examined in hippocampal slices from BAX $-/-$ mice and wild-type littermates. A β failed to block LTP in hippocampal slices from BAX $-/-$ mice, indicating that BAX is essential for A β inhibition of LTP.

Despite much evidence for a central role of amyloid-beta (A β) in the pathogenesis of Alzheimer's disease, the mechanism(s) by which A β produces structural and functional synaptic deficits remain unclear. NMDA receptors are thought to be essential for a number of A β -induced defects in synaptic structure, including degradation of key synaptic proteins, disassembly of the postsynaptic density, and synapse loss¹⁻⁴. However, the role of NMDA receptors in A β -induced changes in functional synaptic plasticity is less clear.

NMDA receptors are heterotetramers made up of two GluN1 (also known as NR1) subunits and two GluN2 (NR2) subunits. GluN2A and GluN2B are the primary NR2 subunits in the hippocampus. A number of recent *in vitro* studies⁵⁻⁷ have examined the role of GluN2B receptors in A β impairment of LTP and reported that GluN2B antagonists prevent disruption of LTP by A β . In the current study, however, we observed only partial attenuation of the A β effect on LTP with Ro25-6981, a GluN2B-selective antagonist. We also treated hippocampal slices with A β in the presence of D-AP5, a broad-spectrum NMDA receptor antagonist. D-AP5 prevented the A β -induced loss of LTP, consistent with results on spine structural plasticity⁸. Thus, our data suggest that both GluN2A and GluN2B can contribute to A β inhibition of LTP.

Emerging evidence indicates that the molecular pathways that classically mediate programmed cell death (apoptosis) can also participate in non-apoptotic functions in neurons, including synaptic plasticity^{9,10}. In particular, caspase-3 activation has been shown to be required for hippocampal long-term depression (LTD)¹¹ and for A β inhibition of hippocampal long-term potentiation (LTP)¹². BAX, a pro-apoptotic member of the Bcl-2 protein family that is upstream of caspase-3 in the intrinsic (mitochondrial) pathway of apoptosis¹³, is also required for NMDA receptor-dependent LTD in hippocampal neurons¹⁴. Is BAX also essential for A β suppression of LTP? We report results in BAX knockout mice that support the conclusion that a common apoptotic pathway is utilized for LTD and A β suppression of LTP.

Results

Effects of A β on synaptic transmission and plasticity in area CA1 of the hippocampus. To determine whether A β affects basal excitatory synaptic transmission, input-output curves were recorded from area CA1 of acute hippocampal slices preincubated with A β (500 nM, 2–3 hours) and untreated control slices. A comparison of the two curves reveals no significant difference in basal synaptic transmission following 2–3 hours of A β pretreatment (Figure 1A). Similarly, there was no difference in paired pulse facilitation between A β -treated slices and untreated slices (Figure 1B).

The effect of A β on synaptic plasticity was also assessed in hippocampal slices. Long-term depression (LTD), induced by 1 Hz stimulation for 15 minutes, was similar in A β -treated and untreated slices (~20% reduction from baseline; Figure 1C). However, when a subthreshold LTD induction protocol was used (1 Hz for 5 min

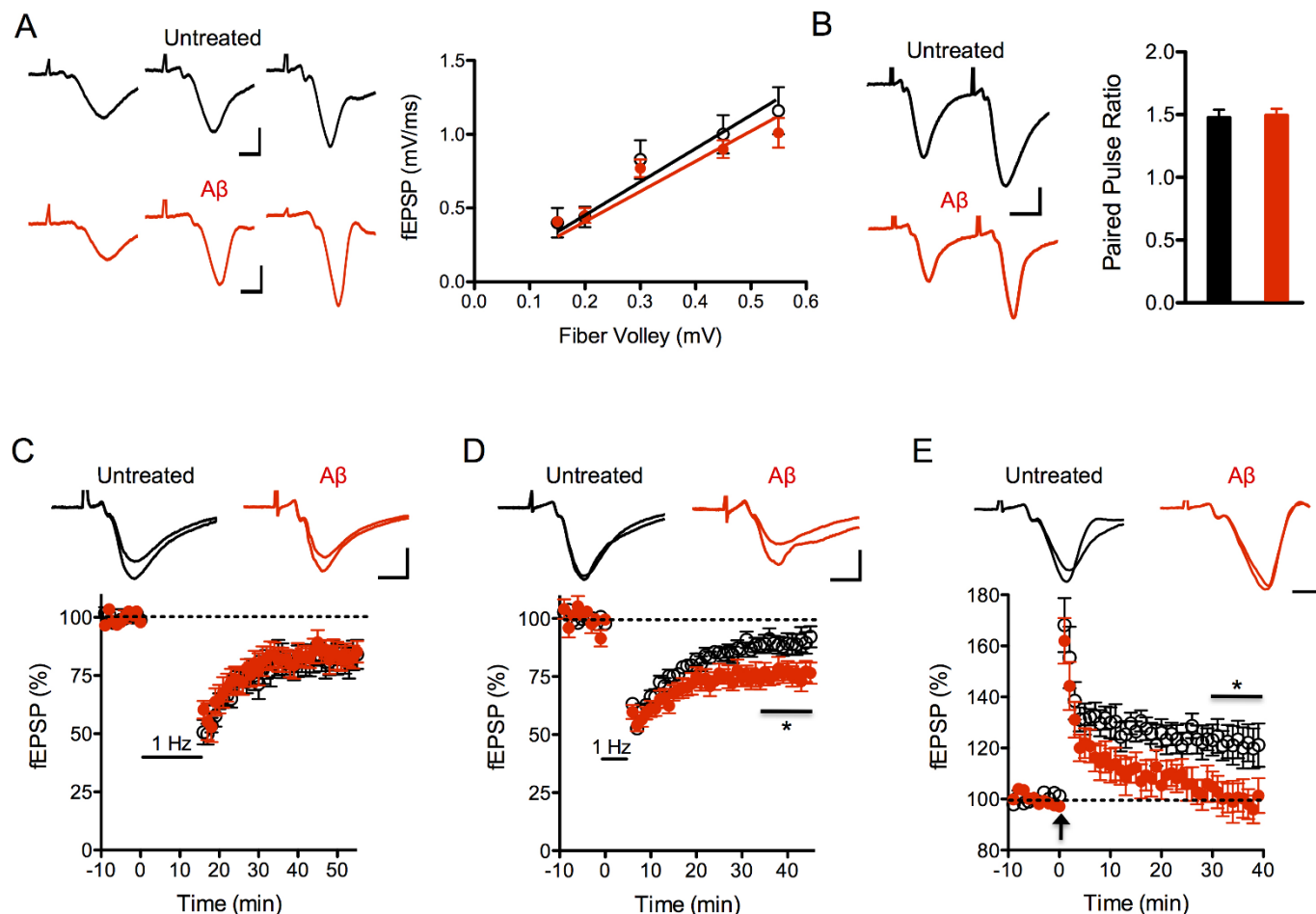


Figure 1 | $A\beta$ enhances LTD and reduces LTP but has no effect on basal synaptic transmission in area CA1 of the hippocampus. (A) Input-output curves were plotted for untreated ($n=3-5$) and $A\beta$ -treated ($n=6-9$) hippocampal slices. Comparison of the two curves reveals no significant difference in basal synaptic transmission ($m=2.3 \pm 0.1$ vs. 2.0 ± 0.1 for untreated and $A\beta$, respectively; $P=0.35$). Sample traces are shown on the left. In these and all subsequent sample traces, the shock artifact has been truncated. Scale bars: 0.7 mV, 3 ms. (B) Paired pulse facilitation (20 ms interspike interval) is unaffected by $A\beta$ treatment ($n=4$ vs. 6 untreated slices; $P=1.00$). Scale bars: 0.5 mV, 7 ms. (C) LTD induced by low-frequency stimulation (1 Hz) for 15 min is similar in untreated ($n=7$) and $A\beta$ -treated ($n=8$) slices ($P=0.80$). In this and all subsequent figures, sample traces represent the 10 min baseline period and the period 30–40 min post LTD or LTP induction. (D) A subthreshold LTD induction protocol (1 Hz, 5 min) induces LTD in $A\beta$ -treated slices ($n=8$) but not in interleaved untreated slices ($n=8$; * $P=0.03$). Scale bars for C and D: 0.5 mV, 5 ms. (E) Theta-burst stimulation (TBS; arrow) induces LTP in untreated slices ($n=6$) but not in interleaved $A\beta$ + picrotoxin-treated slices ($n=6$; * $P=0.04$). Scale bars: 0.4 mV, 3 ms.

rather than 15 min), LTD averaged $\sim 25\%$ in $A\beta$ -treated slices but was absent in untreated slices (Figure 1D), consistent with recent reports^{4,15}. To measure LTP, we applied theta burst stimulation (TBS; 10 bursts at 5 Hz; burst=5 pulses, 100 Hz) after a stable 10-minute baseline period. TBS-induced LTP averaged $122 \pm 7\%$ ($n=6$) of baseline in untreated hippocampal slices but was abolished in $A\beta$ -treated slices ($100 \pm 6\%$; $n=6$; Figure 1E). Because picrotoxin (100 μM) was present during the $A\beta$ preincubation period in these experiments, it appears that $A\beta$ -inhibition of LTP does not reflect excess GABAergic transmission. In sum, exposure to $A\beta$ for 2–3 hours enhances LTD and impairs LTP, without affecting basal synaptic transmission.

NMDA receptors are essential for $A\beta$ -inhibition of LTP. To test the involvement of NMDA receptors in $A\beta$ -mediated suppression of LTP, we added the broad-spectrum NMDA receptor antagonist D-AP5 during the $A\beta$ incubation period, and washed it out for 30 min prior to TBS stimulation (because NMDA receptors are essential for LTP induction). In the presence of D-AP5 (50 μM), $A\beta$ failed to block LTP ($124 \pm 5\%$; $n=6$; Figure 2A). In the same series of experiments, LTP was completely abolished in slices preincubated with $A\beta$ alone ($102 \pm 5\%$; $n=4$). As expected, a two-hour preincubation with D-AP5

alone (followed by a 30 min washout period before LTP induction) had no effect on LTP ($127 \pm 7\%$; $n=4$; Figure 2B). Thus, NMDA receptor activity is required during the $A\beta$ treatment period for suppression of LTP.

The great majority of NMDA receptors in hippocampus are composed of GluN1 subunits combined with either GluN2A or GluN2B subunits. Which subtype of NMDA receptor is required for the $A\beta$ inhibition of LTP? Ro25-6981 (3 μM), a selective GluN2B receptor antagonist, partially attenuated $A\beta$ inhibition of LTP when present during the $A\beta$ incubation ($120 \pm 7\%$ ($n=11$) vs. $134 \pm 8\%$ ($n=10$) in untreated controls; Figure 3A). LTP was not affected by a 2 h preincubation with Ro25-6981 followed by a 30 min washout period before LTP induction ($135 \pm 7\%$; $n=4$; Figure 3B). Ro25-6981 did not reverse $A\beta$ -inhibition of LTP when applied during the LTP induction protocol (i.e. following $A\beta$ incubation; $104 \pm 4\%$; $n=5$; Figure 3C), as opposed to during the $A\beta$ preincubation period. Thus GluN2B NMDA receptors are not required for LTP induction; on the contrary, their activity seems to contribute in part to suppression of LTP by $A\beta$.

$A\beta$ fails to inhibit LTP in hippocampal slices from BAX $-/-$ mice. Caspase-3 knockout mice do not show NMDA receptor dependent

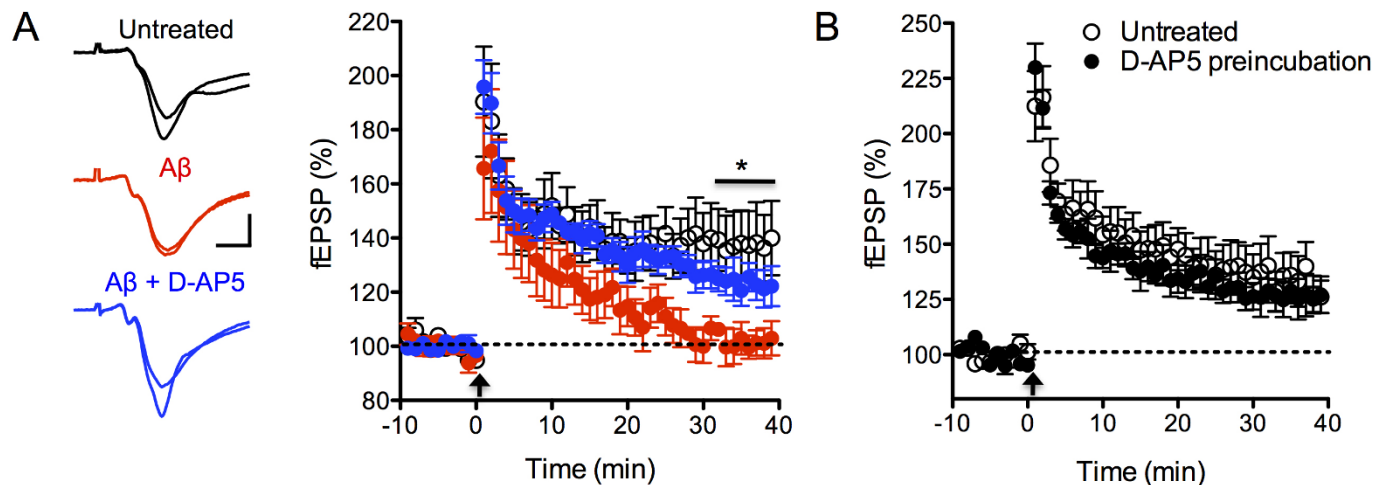


Figure 2 | Inhibition of NMDA receptors during A β -pretreatment rescues A β impairment of LTP. (A) TBS-induced LTP was observed in untreated hippocampal slices ($n=7$) and slices pretreated with A β in the presence of D-AP5 (NMDA receptor antagonist; $n=6$), but LTP was absent in A β -treated slices ($n=4$; $P=0.05$). D-AP5 was washed out for 30 min prior to LTP induction. Sample traces are shown on the left. Scale bars: 0.4 mV, 4 ms for untreated and A β -treated slices; 0.6 mV, 4 ms for A β + D-AP5-treated slices. (B) LTP was unaffected by a 2 hr D-AP5 pretreatment followed by a 30 min washout (untreated $n=7$, D-AP5 $n=4$; $P=0.62$).

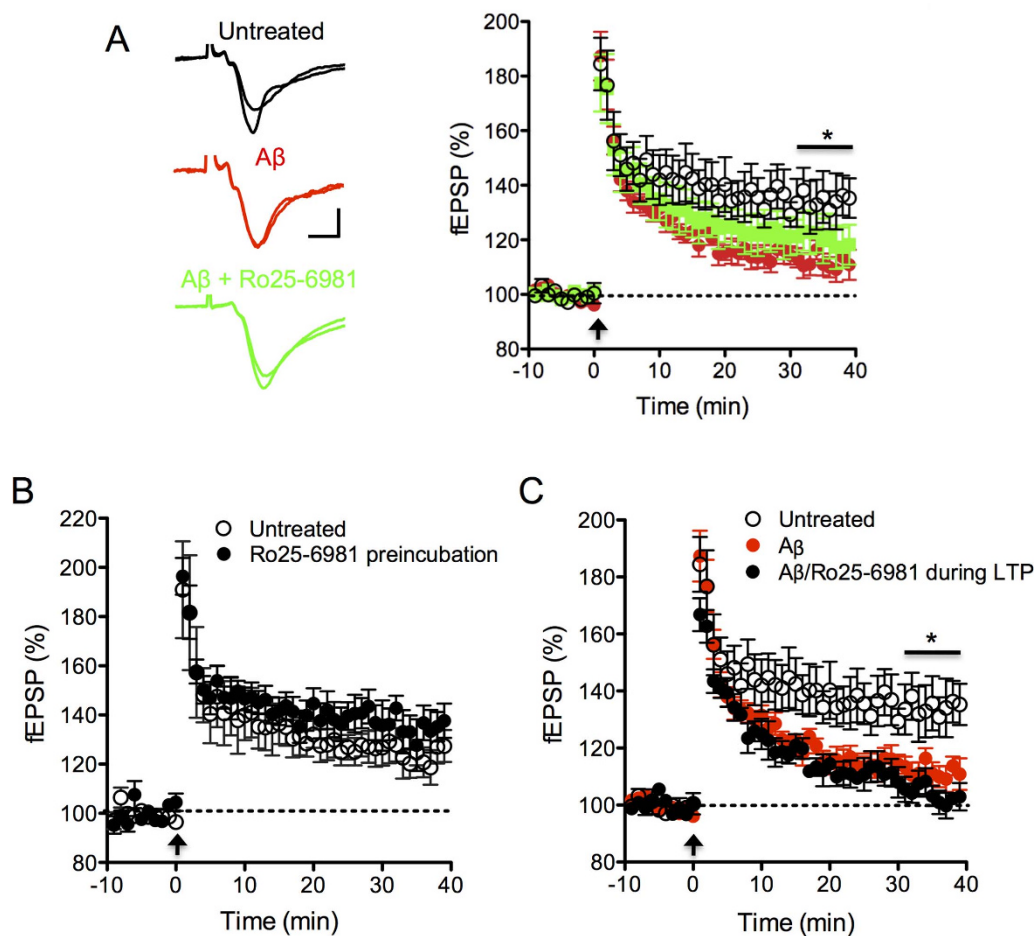


Figure 3 | Inhibition of GluN2B receptors during A β -pretreatment partially rescues A β impairment of LTP. (A) LTP is observed following pretreatment of hippocampal slices with A β in the presence of Ro25-6981 (GluN2B antagonist, $n=11$) but not in A β -treated slices ($n=11$). Ro25-6981 only partially rescues LTP relative to untreated slices ($n=10$; $*P=0.05$). Sample traces before and after LTP are shown on the left. Scale bars: 0.5 mV, 5 ms for untreated and A β + Ro25-6981-treated slices; 0.25 mV, 5 ms for A β -treated slices. (B) A 2 hr pretreatment with Ro25-6981 alone had no effect on LTP ($n=4$ and 5 for Ro25-6981 and untreated, respectively; $P=0.29$). (C) Ro25-6981 failed to rescue LTP when it was applied after A β (i.e. before and during LTP induction/expression; $*P=0.01$). $n=10$, 11 and 5 for untreated, A β and A β preincubation/Ro25-6981 during LTP, respectively.

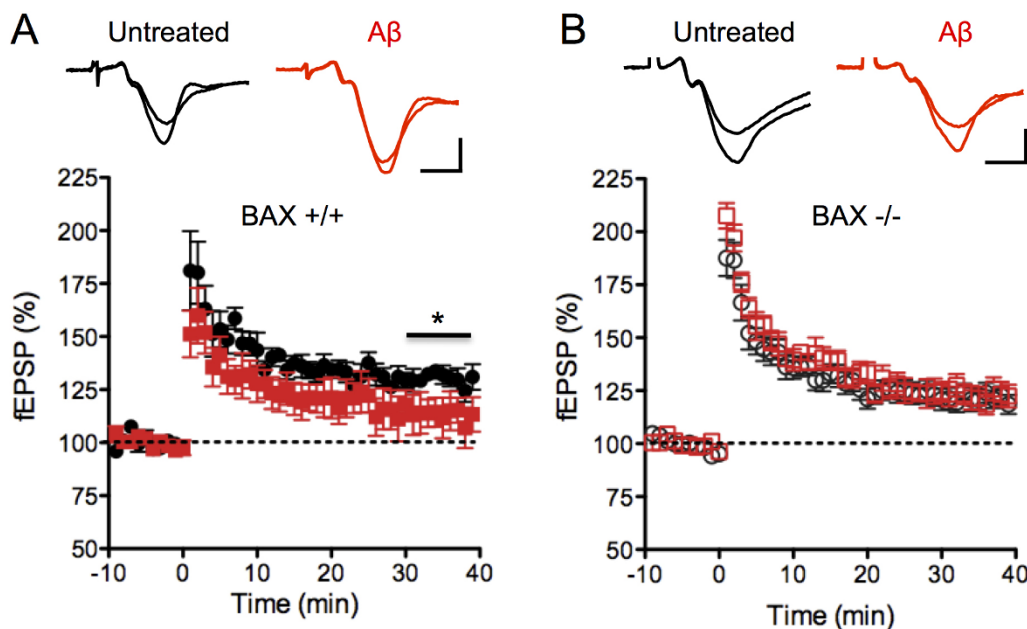


Figure 4 | BAX is essential for A β inhibition of LTP. (A) A β impairs LTP in hippocampal slices from BAX $+/+$ mice ($n=9$ and 5 for untreated and A β -treated slices, respectively; * $P=0.03$). (B) A β does not impair LTP in hippocampal slices from BAX $-/-$ mice ($n=12$ and 8 untreated and A β -treated slices, respectively; $P=0.89$). Sample traces from BAX $+/+$ and BAX $-/-$ hippocampal slices are shown above. Scale bars (A and B): 0.4 mV, 4 ms.

LTD or A β suppression of LTP^{11,12}. Knockout mice lacking BAX, a protein upstream in the mitochondrial pathway of apoptosis, lack LTD in hippocampus¹⁴. Are these mice also protected from A β suppression of LTP? We found that CA1 LTP is similar in hippocampal slices from BAX $-/-$ and $+/+$ littermates ($121 \pm 4\%$ vs. $130 \pm 4\%$, $n=12$ and 9 , respectively; $P=0.25$; Figure 4). As expected, LTP was significantly reduced following A β pretreatment of BAX $+/+$ slices (112 ± 8 ; $n=5$; Figure 4A). In hippocampal slices from BAX $-/-$ littermates, however, LTP was unaffected by A β (122 ± 5 ; $n=8$; Figure 4B). Thus, BAX is required for A β inhibition of LTP, as it is for LTD.

Discussion

We find that A β inhibits LTP and enhances LTD without disrupting basal synaptic transmission. Because D-AP5 – when coapplied with A β – largely blocks A β inhibition of LTP, we conclude that NMDA receptor activity is critical for A β 's ability to suppress LTP. Attenuation of A β inhibition of LTP by the GluN2B (NR2B)-selective antagonist Ro25-6981 has been reported *in vivo*¹⁶ and *in vitro* in hippocampal slices from 6-week to 4-month-old mice⁵⁻⁷. In the current study, LTP was only partially rescued when hippocampal slices from 4- to 5-week-old mice were incubated with Ro25-6981 together with A β . During postnatal development, the GluN2 subunit composition of NMDA receptors progressively changes from GluN2B to GluN2A¹⁷⁻¹⁹. This developmental 'switch' could account for the more subtle Ro25-6981 effect we observe in younger slices. However, if anything, the somewhat less mature hippocampal slices that were used in the current study should have more GluN2B subunits and, thus, should be more sensitive to Ro25-6981. Therefore, our results suggest that NMDA receptors insensitive to Ro25-6981 (possibly GluN2A-containing NMDA receptors) may also contribute to suppression of LTP by A β .

A β can directly activate recombinant GluN2A and GluN2B receptors in heterologous expression systems²⁰. A β may act similarly in neurons, though evidence for such direct action is lacking. A β may promote synaptic glutamate release^{21,22} or impair glutamate reuptake^{23,24}, which indirectly leads to aberrant NMDA receptor activation, especially of extrasynaptic GluN2B NMDA receptors¹⁵. A β has also been shown to cause synaptotoxic stimulation of metabotropic

glutamate receptors (mGluR5)²⁵, which can functionally interact with NMDA receptors.

How might aberrant NMDA receptor activation by A β lead to impairment of LTP? Recent evidence has pointed to the mitochondrial apoptosis pathway as being critical for NMDA receptor-dependent LTD and there are emerging mechanistic links between LTD and A β -mediated suppression of synaptic function^{11,12,14,26,27}. We found that knockout mice lacking BAX – a Bcl2 family protein required for mitochondrial membrane permeabilization and the intrinsic apoptosis pathway – no longer show A β suppression of LTP, while LTP *per se* is normal. Together with recent findings that NMDA receptor stimulation leads to significant activation of the caspase-3 cascade^{11,14}, our data provide additional compelling evidence that the mitochondrial pathway of apoptosis is centrally involved in the synaptotoxic action of A β .

Overactivation of NMDA receptors is often associated with excitotoxic cell death and synaptic depression²⁸. However, we observed that acute A β treatment disrupts LTP in a NMDA receptor-dependent fashion in the absence of cell death or even weakening of basal synaptic transmission. BAX activation of caspase-3 has been linked to non-apoptotic functions in addition to programmed cell death^{13,14}. Analogous to caspase-3^{11,12}, BAX plays a role in LTD induction¹⁴ and A β -inhibition of LTP (Figure 4). Thus, mediators classically associated with apoptosis may play critical non-apoptotic roles in the pathophysiology of Alzheimer's disease, and as such, may serve as potential therapeutic targets in this and other neurodegenerative diseases.

The molecular mechanisms by which activation of the apoptotic pathway and caspase-3 lead to synaptic dysfunction remain unclear. Intriguing data suggest that tau – a protein highly implicated in the pathology of Alzheimer's disease and other neurodegenerative disorders²⁹ – is required for impaired LTP in mouse models of Alzheimer's disease³⁰ and A β -treated hippocampal slices³¹. Caspase-3 can cleave tau at a specific site, which promotes tau aggregation^{32,33}. Accumulation of dendritic tau may favor the interaction between PSD-95 and NMDA receptors, thereby promoting excitotoxicity³⁴. Whether such a mechanism mutually links NMDA receptors and the apoptotic cascade, and whether this mechanism contributes to A β impairment of LTP, remains to be elucidated.



Methods

Electrophysiology. Transverse hippocampal slices (400 μm thick) were prepared from 2- to 3-week-old mice for LTD experiments and 4- to 5-week-old mice for all other experiments. Slices were cut in artificial cerebrospinal fluid (ACSF), which contained (in mM): 119 NaCl, 2.5 KCl, 1.3 MgSO_4 , 2.5 CaCl_2 , 1 NaH_2PO_4 , 26 NaHCO_3 and 11 glucose, equilibrated with 95% O_2 /5% CO_2 . Slices were allowed to recover in ACSF for 45 min at 37°C followed by ≥ 1 -hour incubation at room temperature. Following the recovery period, slices were incubated with $\text{A}\beta$ (500 nM) or $\text{A}\beta$ + NMDA receptor antagonist. Two to three hours later, slices were transferred to a submerged recording chamber mounted on an Olympus dissecting microscope. Untreated control slices or slices treated with NMDA receptor antagonist were interleaved with $\text{A}\beta$ -treated slices. For experiments with BAX $-/-$ mice, slices from BAX $+/+$ littermates were interleaved.

A glass pipette filled with ACSF was used to stimulate the Schaffer collaterals and field excitatory postsynaptic potentials (fEPSPs) were recorded extracellularly in area CA1 at room temperature using low-resistance patch pipettes filled with ACSF. The baseline stimulation rate was 0.05 Hz. fEPSPs were filtered at 2 kHz and digitized at 10 kHz with a Multiclamp (Molecular Devices, Sunnyvale, CA). Data were collected and analyzed with pClamp 10.2.0.12 software (Molecular Devices). Fiber volley amplitude was measured peak-to-peak. The slope of the initial rising phase (20–60% of the peak amplitude) of the fEPSP was used as a measure of the postsynaptic response. All data are expressed as mean \pm SEM. Student's *t*-test and one-way ANOVA were used to measure statistical significance. $P \leq 0.05$ was considered significant.

BAX null mice. BAX knockout mice were obtained from Stanley Korsmeyer³⁵ and were bred/maintained at Genentech in accordance with the guidelines set forth by our Institutional Animal Care and Use Committee.

Reagents. Soluble oligomeric $\text{A}\beta_{1-42}$ (mostly ranging from 2-mer to 6-mer¹²) was prepared according to the manufacturer's instructions (Ascent Scientific, Princeton, NJ). Briefly, $\text{A}\beta$ (1 mg/ml) was dissolved in 1, 1, 1, 3, 3, 3 - hexafluoro-2-propanol (HFIP; Sigma, St. Louis, MO), incubated at room temperature for 1 hr with occasional vortexing, and then sonicated for 10 min. The solution was dried under a gentle stream of nitrogen gas, then resuspended in 100% DMSO and incubated for 12 min at room temperature. This $\text{A}\beta$ stock solution was aliquoted and stored at -80°C . On each experimental day, an aliquot of $\text{A}\beta$ stock solution was diluted to 500 nM with D-PBS (Invitrogen, Carlsbad, CA) and incubated for 2 hr at room temperature to permit peptide aggregation.

The following drugs, prepared daily from concentrated ($\geq 1000\times$) stock solutions, were also used in this study: picrotoxin (Tocris, Ellisville, MO), D-AP5 (Tocris) and Ro25-6981 (synthesized in-house).

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Author contributions

KMO and MS conceived of the experiments and wrote the manuscript. KMO performed the experiments.

Additional information

Competing financial interests: The authors declare no competing financial interests.

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