SCIENTIFIC REPORTS

SUBJECT AREAS:
PLASTICITY
SYNAPTIC TRANSMISSION
CELLULAR NEUROSCIENCE
NEURODEGENERATION

Received
19 September 2011

Accepted
22 December 2011

Published
16 January 2012

Correspondence and requests for materials should be addressed to M.S. (sheng.morgan@gene.com) or K.M.O. (kolsen@rockefeller.edu)

* Current address: Rockefeller University 1230 York Avenue New York

NMDA receptors and BAX are essential for Aβ impairment of LTP

Kimberly Moore Olsen* & Morgan Sheng

Department of Neuroscience, Genentech Inc. 1 DNA Way South San Francisco, CA 94080 USA.

Accumulation of amyloid-β (Aβ) 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 Aβ 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 Aβ-mediated inhibition of LTP in area CA1 of the hippocampus. Ro25-6981, an antagonist selective for GluN2B (NR2B) NMDA receptors, only partially prevented this Aβ action, suggesting that GluN2A and GluN2B receptors may both contribute to Aβ suppression of LTP. The effect of Aβ on LTP was also examined in hippocampal slices from BAX −/− mice and wild-type littermates. Aβ failed to block LTP in hippocampal slices from BAX −/− mice, indicating that BAX is essential for Aβ inhibition of LTP.

Despite much evidence for a central role of amyloid-beta (Aβ) in the pathogenesis of Alzheimer's disease, the mechanism(s) by which Aβ produces structural and functional synaptic deficits remain unclear. NMDA receptors are thought to be essential for a number of Aβ-induced defects in synaptic structure, including degradation of key synaptic proteins, disassembly of the postsynaptic density, and synapse loss[1–4]. However, the role of NMDA receptors in Aβ-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* studies[5–7] have examined the role of GluN2B receptors in Aβ impairment of LTP and reported that GluN2B antagonists prevent disruption of LTP by Aβ. In the current study, however, we observed only partial attenuation of the Aβ effect on LTP with Ro25-6981, a GluN2B-selective antagonist. We also treated hippocampal slices with Aβ in the presence of D-AP5, a broad-spectrum NMDA receptor antagonist. D-AP5 prevented the Aβ-induced loss of LTP, consistent with results on spine structural plasticity[8]. Thus, our data suggest that both GluN2A and GluN2B can contribute to Aβ 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 Aβ 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 apoptosis[13], is also required for NMDA receptor-dependent LTD in hippocampal neurons[14]. Is BAX also essential for Aβ suppression of LTP? We report results in BAX knockout mice that support the conclusion that a common apoptotic pathway is utilized for LTD and Aβ suppression of LTP.

Results

Effects of Aβ on synaptic transmission and plasticity in area CA1 of the hippocampus. To determine whether Aβ affects basal excitatory synaptic transmission, input-output curves were recorded from area CA1 of acute hippocampal slices preincubated with Aβ (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 Aβ pretreatment (Figure 1A). Similarly, there was no difference in paired pulse facilitation between Aβ-treated slices and untreated slices (Figure 1B).

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

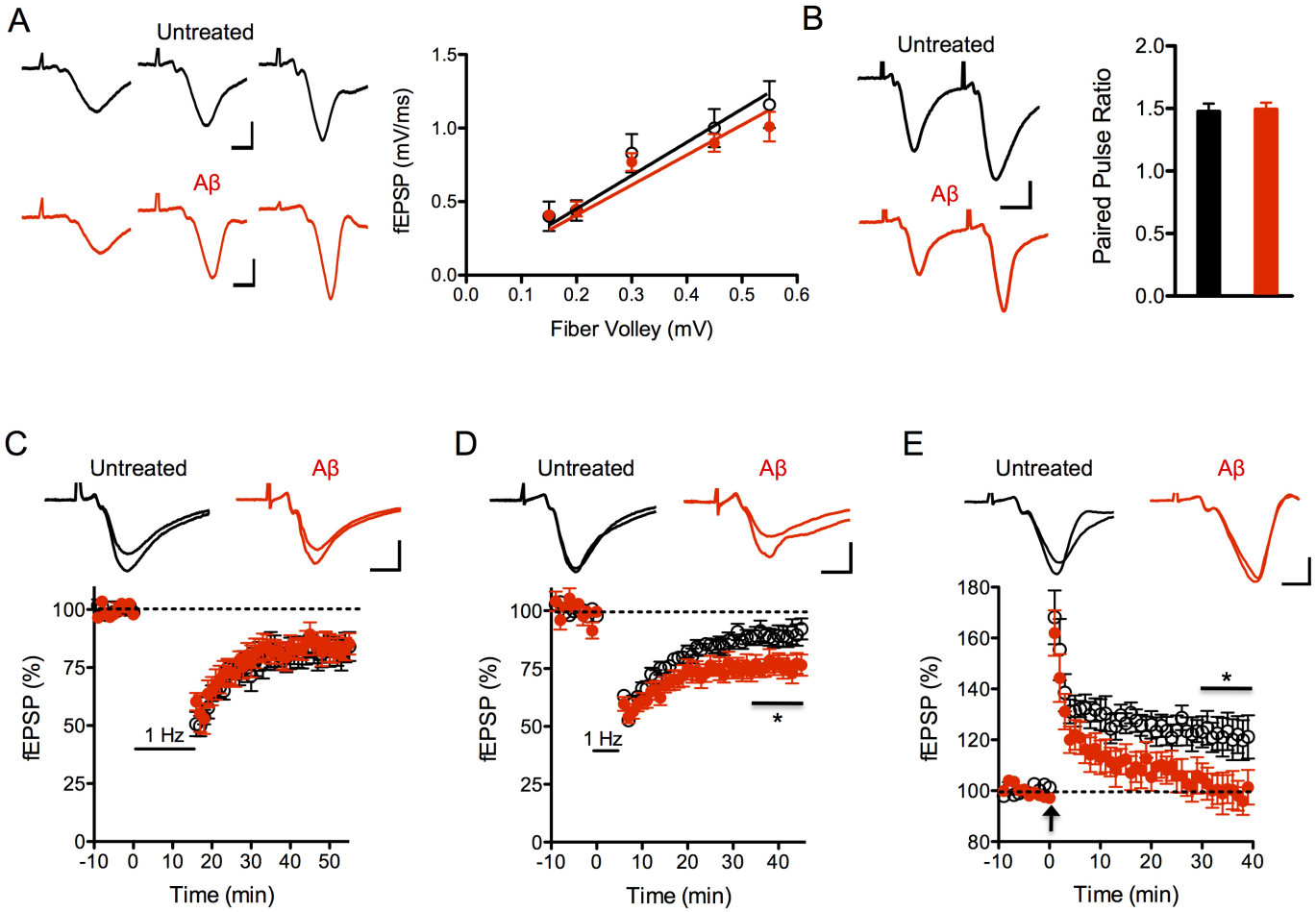

Figure 1 | Aβ enhances LTD and reduces LTP but has no effect on basal synaptic transmission in area CA1 of the hippocampus. (A) Input-output curves were plotted for untreated (n=3−5) and Aβ-treated (n=6−9) hippocampal slices. Comparison of the two curves reveals no significant difference in basal synaptic transmission (m=2.3 ± 0.1 vs. 2.0 ± 0.1 for untreated and Aβ, 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 Aβ 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 Aβ-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 Aβ-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 Aβ + picrotoxin-treated slices (n=6; * P=0.04). Scale bars: 0.4 mV, 3 ms.

rather than 15 min), LTD averaged ~25% in Aβ-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 ± 7% (n=6) of baseline in untreated hippocampal slices but was abolished in Aβ-treated slices (100 ± 6%; n=6; Figure 1E). Because picrotoxin (100 μM) was present during the Aβ preincubation period in these experiments, it appears that Aβ-inhibition of LTP does not reflect excess GABAergic transmission. In sum, exposure to Aβ for 2–3 hours enhances LTD and impairs LTP, without affecting basal synaptic transmission.

NMDA receptors are essential for Aβ-inhibition of LTP. To test the involvement of NMDA receptors in Aβ-mediated suppression of LTP, we added the broad-spectrum NMDA receptor antagonist D-AP5 during the Aβ 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), Aβ failed to block LTP (124 ± 5%; n=6; Figure 2A). In the same series of experiments, LTP was completely abolished in slices preincubated with Aβ alone (102 ± 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 ± 7%; n=4; Figure 2B). Thus, NMDA receptor activity is required during the Aβ 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 Aβ inhibition of LTP? Ro25-6981 (3 μM), a selective GluN2B receptor antagonist, partially attenuated Aβ inhibition of LTP when present during the Aβ incubation (120 ± 7% (n=11) vs. 134 ± 8% (n=10) in untreated controls; Figure 3A). LTP was not affected by a 2 h pre-incubation with Ro25-6981 followed by a 30 min washout period before LTP induction (135 ± 7%; n=4; Figure 3B). Ro25-6981 did not reverse Aβ-inhibition of LTP when applied during the LTP induction protocol (i.e. following Aβ incubation; 104 ± 4%; n=5; Figure 3C), as opposed to during the Aβ 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 Aβ.

Aβ fails to inhibit LTP in hippocampal slices from BAX −/− mice. Caspase-3 knockout mice do not show NMDA receptor dependent

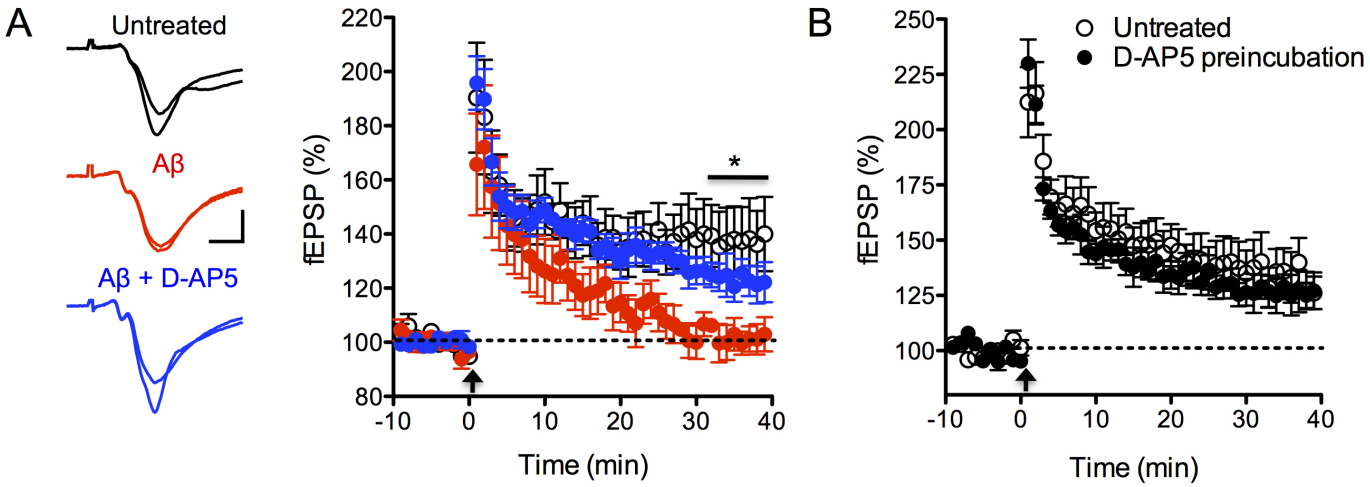

Figure 2 | Inhibition of NMDA receptors during Aβ-pretreatment rescues Aβ impairment of LTP. (A) TBS-induced LTP was observed in untreated hippocampal slices (n=7) and slices pretreated with Aβ in the presence of D-AP5 (NMDA receptor antagonist; n=6), but LTP was absent in Aβ-treated slices (n=4; P=0.05). 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 Aβ-treated slices; 0.6 mv, 4 ms for Aβ + 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).

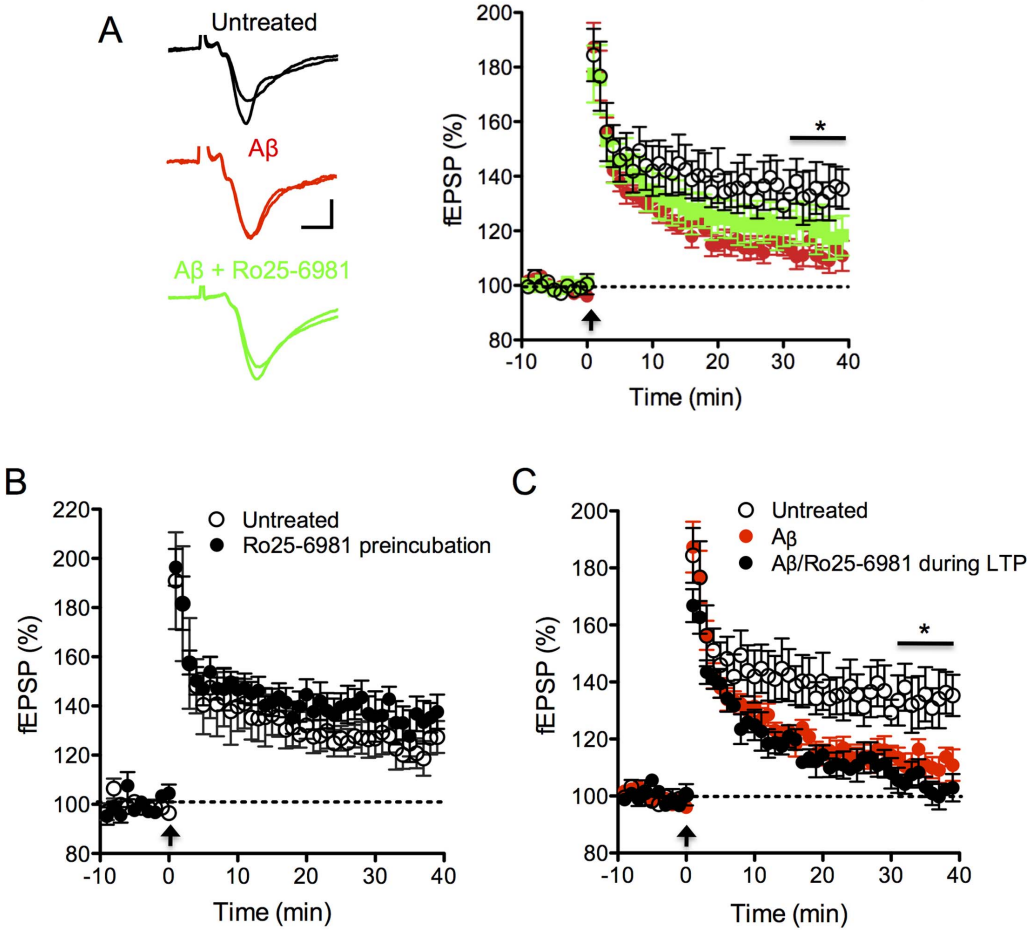

Figure 3 | Inhibition of GluN2B receptors during Aβ-pretreatment partially rescues Aβ impairment of LTP. (A) LTP is observed following pretreatment of hippocampal slices with Aβ in the presence of Ro25-6981 (GluN2B antagonist, n=11) but not in Aβ-treated slices (n=11). Ro25-6981 only partially rescues 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 Aβ + Ro25-6981−treated slices; 0.25 mV, 5 ms for Aβ-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 Aβ (i.e. before and during LTP induction/expression; * P=0.01). n=10, 11 and 5 for untreated, Aβ and Aβ preincubation/Ro25-6981 during LTP, respectively.

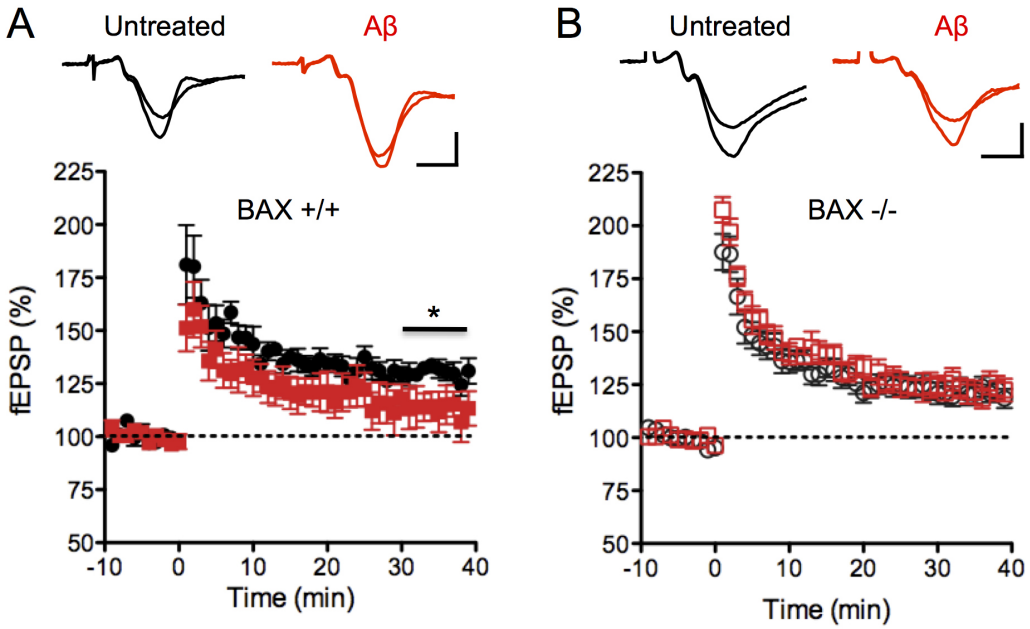

Figure 4 | BAX is essential for Aβ inhibition of LTP. (A) Aβ impairs LTP in hippocampal slices from BAX +/+ mice (n=9 and 5 for untreated and Aβ-treated slices, respectively; * P=0.03). (B) Aβ does not impair LTP in hippocampal slices from BAX −/− mice (n=12 and 8 untreated and Aβ-treated slices, respectively; 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 Aβ suppression of LTP[11,12]. Knockout mice lacking BAX, a protein upstream in the mitochondrial pathway of apoptosis, lack LTD in hippocampus[14]. Are these mice also protected from Aβ suppression of LTP? We found that CA1 LTP is similar in hippocampal slices from BAX −/− and +/+ littermates (121 ± 4% vs. 130 ± 4%, n=12 and 9, respectively; P=0.25; Figure 4). As expected, LTP was significantly reduced following Aβ pretreatment of BAX +/+ slices (112 ± 8; n=5; Figure 4A). In hippocampal slices from BAX −/− littermates, however, LTP was unaffected by Aβ (122 ± 5; n=8; Figure 4B). Thus, BAX is required for Aβ inhibition of LTP, as it is for LTD.

Discussion

We find that Aβ inhibits LTP and enhances LTD without disrupting basal synaptic transmission. Because D-AP5 − when coapplied with Aβ − largely blocks Aβ inhibition of LTP, we conclude that NMDA receptor activity is critical for Aβ's ability to suppress LTP. Attenuation of Aβ 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 mice[5–7]. 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 Aβ. During postnatal development, the GluN2 subunit composition of NMDA receptors progressively changes from GluN2B to GluN2A[17–19]. 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 Aβ.

Aβ can directly activate recombinant GluN2A and GluN2B receptors in heterologous expression systems[20]. Aβ may act similarly in neurons, though evidence for such direct action is lacking. Aβ 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 receptors[15]. Aβ 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 Aβ 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 Aβ-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 Aβ 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 Aβ.

Overactivation of NMDA receptors is often associated with excitotoxic cell death and synaptic depression[28]. However, we observed that acute Aβ 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 induction[14] and Aβ-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 disorders[29] – is required for impaired LTP in mouse models of Alzheimer's disease[30] and Aβ-treated hippocampal slices[31]. 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 excitotoxicity[34]. Whether such a mechanism mutually links NMDA receptors and the apoptotic cascade, and whether this mechanism contributes to Aβ 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% 0_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 Aβ (500 nM) or Aβ + 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 Aβ-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 ± SEM. Student's *t*-test and one-way ANOVA were used to measure statistical significance. P≤0.05 was considered significant.

BAX null mice. BAX knockout mice were obtained from Stanley Korsemeyer[35] and were bred/maintained at Genentech in accordance with the guidelines set forth by our Institutional Animal Care and Use Committee.

Reagents. Soluble oligomeric $A\beta_{1-42}$ (mostly ranging from 2-mer to 6-mer[12]) was prepared according to the manufacturer's instructions (Ascent Scientific, Princeton, NJ). Briefly, Aβ (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 Aβ stock solution was aliquoted and stored at –80°C. On each experimental day, an aliquot of Aβ 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 (≥ 1000 ×) stock solutions, were also used in this study: picrotoxin (Tocris, Ellisville, MO), D-AP5 (Tocris) and Ro25-6981 (synthesized in-house).

1. Liu, J. *et al.* Amyloid-beta induces caspase-dependent loss of PSD-95 and synaptophysin through NMDA receptors. *J Alzheimers Dis* **22**, 541–556 (2010).
2. Roselli, F., Hutzler, P., Wegerich, Y., Livrea, P. & Almeida, O. F. Disassembly of shank and homer synaptic clusters is driven by soluble beta-amyloid(1–40) through divergent NMDAR-dependent signalling pathways. *PLoS One* **4**, e6011 (2009).
3. Shankar, G. M. *et al.* Natural oligomers of the Alzheimer amyloid-beta protein induce reversible synapse loss by modulating an NMDA-type glutamate receptor-dependent signaling pathway. *J Neurosci* **27**, 2866–2875 (2007).
4. Shankar, G. M. *et al.* Amyloid-beta protein dimers isolated directly from Alzheimer's brains impair synaptic plasticity and memory. *Nat Med* **14**, 837–842 (2008).
5. Ronicke, R. *et al.* Early neuronal dysfunction by amyloid beta oligomers depends on activation of NR2B-containing NMDA receptors. *Neurobiol Aging* **32**, 2219–2228 (2011).
6. Rammes, G., Hasenjager, A., Sroka-Saidi, K., Deussing, J. M. & Parsons, C. G. Therapeutic significance of NR2B-containing NMDA receptors and mGluR5 metabotropic glutamate receptors in mediating the synaptotoxic effects of beta-amyloid oligomers on long-term potentiation (LTP) in murine hippocampal slices. *Neuropharmacology* **60**, 982–990 (2011).
7. Li, S. *et al.* Soluble Abeta oligomers inhibit long-term potentiation through a mechanism involving excessive activation of extrasynaptic NR2B-containing NMDA receptors. *J Neurosci* **31**, 6627–6638 (2011).
8. Wei, W. *et al.* Amyloid beta from axons and dendrites reduces local spine number and plasticity. *Nat Neurosci* **13**, 190–196 (2010).
9. D'Amelio, M., Cavallucci, V. & Cecconi, F. Neuronal caspase-3 signaling: not only cell death. *Cell Death Differ* **17**, 1104–1114 (2010).
10. Yates, D. Synaptic plasticity: finely tuning caspase function. *Nat Rev Neurosci* **12**, 371 (2011).
11. Li, Z. *et al.* Caspase-3 activation via mitochondria is required for long-term depression and AMPA receptor internalization. *Cell* **141**, 859–871 (2010).
12. Jo, J. *et al.* Abeta(1–42) inhibition of LTP is mediated by a signaling pathway involving caspase-3, Akt1 and GSK-3beta. *Nat Neurosci* **14**, 545–547 (2011).
13. Youle, R. J. & Strasser, A. The BCL-2 protein family: opposing activities that mediate cell death. *Nat Rev Mol Cell Biol* **9**, 47–59 (2008).
14. Jiao, S. & Li, Z. Nonapoptotic function of BAD and BAX in long-term depression of synaptic transmission. *Neuron* **70**, 758–772 (2011).
15. Li, S. *et al.* Soluble oligomers of amyloid Beta protein facilitate hippocampal long-term depression by disrupting neuronal glutamate uptake. *Neuron* **62**, 788–801 (2009).
16. Hu, N. W., Klyubin, I., Anwyl, R. & Rowan, M. J. GluN2B subunit-containing NMDA receptor antagonists prevent Abeta-mediated synaptic plasticity disruption in vivo. *Proc Natl Acad Sci U S A* **106**, 20504–20509 (2009).
17. Monyer, H., Burnashev, N., Laurie, D. J., Sakmann, B. & Seeburg, P. H. Developmental and regional expression in the rat brain and functional properties of four NMDA receptors. *Neuron* **12**, 529–540 (1994).
18. Sheng, M., Cummings, J., Roldan, L. A., Jan, Y. N. & Jan, L. Y. Changing subunit composition of heteromeric NMDA receptors during development of rat cortex. *Nature* **368**, 144–147 (1994).
19. Kirson, E. D. & Yaari, Y. Synaptic NMDA receptors in developing mouse hippocampal neurones: functional properties and sensitivity to ifenprodil. *J Physiol* **497 (Pt 2)**, 437–455 (1996).
20. Texido, L., Martin-Satue, M., Alberdi, E., Solsona, C. & Matute, C. Amyloid beta peptide oligomers directly activate NMDA receptors. *Cell Calcium* **49**, 184–190 (2011).
21. Arias, C., Arrieta, I. & Tapia, R. beta-Amyloid peptide fragment 25–35 potentiates the calcium-dependent release of excitatory amino acids from depolarized hippocampal slices. *J Neurosci Res* **41**, 561–566 (1995).
22. Kabogo, D., Rauw, G., Amritraj, A., Baker, G. & Kar, S. ss-amyloid-related peptides potentiate K+-evoked glutamate release from adult rat hippocampal slices. *Neurobiol Aging* **31**, 1164–1172 (2010).
23. Fernandez-Tome, P., Brera, B., Arevalo, M. A. & de Ceballos, M. L. Beta-amyloid25-35 inhibits glutamate uptake in cultured neurons and astrocytes: modulation of uptake as a survival mechanism. *Neurobiol Dis* **15**, 580–589 (2004).
24. Matos, M., Augusto, E., Oliveira, C. R. & Agostinho, P. Amyloid-beta peptide decreases glutamate uptake in cultured astrocytes: involvement of oxidative stress and mitogen-activated protein kinase cascades. *Neuroscience* **156**, 898–910 (2008).
25. Renner, M. *et al.* Deleterious effects of amyloid beta oligomers acting as an extracellular scaffold for mGluR5. *Neuron* **66**, 739–754 (2010).
26. Kamenetz, F. *et al.* APP processing and synaptic function. *Neuron* **37**, 925–937 (2003).
27. Hsieh, H. *et al.* AMPAR removal underlies Abeta-induced synaptic depression and dendritic spine loss. *Neuron* **52**, 831–843 (2006).
28. Hu, N. W., Ondrejcak, T. & Rowan, M. J. Glutamate receptors in preclinical research on Alzheimer's disease: Update on recent advances. *Pharmacol Biochem Behav* (2011).
29. Morris, M., Maeda, S., Vossel, K. & Mucke, L. The many faces of tau. *Neuron* **70**, 410–426 (2011).
30. Roberson, E. D. *et al.* Amyloid-beta/Fyn-induced synaptic, network, and cognitive impairments depend on tau levels in multiple mouse models of Alzheimer's disease. *J Neurosci* **31**, 700–711 (2011).
31. Shipton, O. A. *et al.* Tau protein is required for amyloid {beta}-induced impairment of hippocampal long-term potentiation. *J Neurosci* **31**, 1688–1692 (2011).
32. Rissman, R. A. *et al.* Caspase-cleavage of tau is an early event in Alzheimer disease tangle pathology. *J Clin Invest* **114**, 121–130 (2004).
33. de Calignon, A. *et al.* Caspase activation precedes and leads to tangles. *Nature* **464**, 1201–1204 (2010).
34. Ittner, L. M. *et al.* Dendritic function of tau mediates amyloid-beta toxicity in Alzheimer's disease mouse models. *Cell* **142**, 387–397 (2010).
35. Knudson, C. M., Tung, K. S., Tourtellotte, W. G., Brown, G. A. & Korsmeyer, S. J. Bax-deficient mice with lymphoid hyperplasia and male germ cell death. *Science* **270**, 96–99 (1995).

Acknowledgements

We wish to thank members of the Sheng lab and Neurophysiology group for helpful discussion during the course of this study.

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 completing financial interests.

How to cite this article: Olsen, K.M. & Sheng, M. NMDA receptors and BAX are essential for Aβ impairment of LTP. *Sci. Rep.* **2**, 225; DOI:10.1038/srep00225 (2012).