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Epilepsy and Cognitive Impairments in Alzheimer Disease

Jorge J. Palop and **Lennart Mucke**
Gladstone Institute of Neurological Disease and Department of Neurology, University of California, San Francisco

Summary

Alzheimer disease (AD) is associated with cognitive decline and increased incidence of seizures. Seizure activity in AD has been widely interpreted as a secondary process resulting from advanced stages of neurodegeneration, perhaps in combination with other age-related factors. However, recent findings in animal models of AD have challenged this notion, raising the possibility that aberrant excitatory neuronal activity represents a primary upstream mechanism that may contribute to cognitive deficits in these models. The following observations suggest that such activity may play a similar role in humans with AD: (1) patients with sporadic AD have an increased incidence of seizures that appears to be independent of disease stage and highest in cases with early onset; (2) seizures are part of the natural history of many pedigrees with autosomal dominant early-onset AD, including those with mutations in presenilin-1, presenilin-2, or the amyloid precursor protein, or with duplications of wild-type amyloid precursor protein; (3) inheritance of the major known genetic risk factor for AD, apolipoprotein E4, is associated with subclinical epileptiform activity in carriers without dementia; and (4) some cases of episodic amnestic wandering and disorientation in AD are associated with epileptiform activity and can be prevented with antiepileptic drugs. Here we review recent experimental data demonstrating that high levels of β-amyloid in the brain can cause epileptiform activity and cognitive deficits in transgenic mouse models of AD. We conclude that β-amyloid peptides may contribute to cognitive decline in AD by eliciting similar aberrant neuronal activity in humans and discuss potential clinical and therapeutic implications of this hypothesis.

Introduction

Alzheimer disease (AD) is associated with increased cerebral levels of β-amyloid (Aβ) peptides, which are derived from the larger amyloid precursor protein (APP) by proteolytic cleavage. The hippocampus and entorhinal cortex play key roles in learning and memory and are primary targets of functional and pathological alterations in AD. Alzheimer disease is also associated with an increased incidence of unprovoked seizures.[1–3] Although neurodegeneration and aging-related cofactors may contribute to the development of seizures in AD, recent data obtained in transgenic mice expressing human APP (hAPP) in neurons indicate that high levels of Aβ are sufficient to elicit epileptiform activity and seizures, even at early stages of the disease process and in the absence of overt neuronal loss.[4] Notably, experimental manipulations that prevent seizure activity in hAPP mice also prevented cognitive deficits in these models.[5] Confirmation of a causal relationship between Aβ-induced aberrant excitatory neuronal activity and cognitive decline in humans with AD would provide important insights into the pathogenesis of AD and could open new therapeutic avenues.

Correspondence: Jorge J. Palop, PhD, or Lennart Mucke, MD, Gladstone Institute of Neurological Disease, San Francisco, CA 94158 (jpalop@gladstone.ucsf.edu or lmucke@gladstone.ucsf.edu)..
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Using Mouse Models to Elucidate Human Disease

Obviously mice are not people, just as apples are not planets. Nonetheless, because apples and planets both have mass, falling apples allowed Newton to elucidate the forces underlying planetary movements. In a similar vein, mice and people share several characteristics that make mice reasonable models for exploring human diseases. Indeed, evolutionary pressures have preserved many processes across mammalian species. An example is spatial learning and memory, which are essential for any species that must return to its home after foraging for food. Humans with AD and hAPP transgenic mice both show navigational deficits that are closely related to impairments of the hippocampus and entorhinal cortex.[6–7]

Although mice never develop AD-like pathology spontaneously, the murine brain is similar enough to the human brain to develop many AD-like changes when exposed to high levels of human Aβ, including amyloid plaques, neuritic dystrophy, gliosis, synaptic deficits, and a range of cognitive and noncognitive behavioral alterations.[5, 8–17] Notably, some alterations or associations were discovered in hAPP mice and subsequently identified for the first time in humans with AD, including loss of calbindin levels in the dentate gyrus[10] and the relation between transforming growth factor β and cerebral amyloid angiopathy.[18]

While none of the available singly transgenic models recapitulates the full spectrum of the human disease, they make it possible to dissect the complexity of AD and to assess the relative pathogenic impact of individual factors in vivo. Compound transgenic mice combining different factors suspected of pathogenic roles in AD or related conditions have shed light on synergisms between Aβ and apolipoprotein (apo) E4,[19] Aβ and tau,[5, 20] and Aβ and {alpha}-synuclein.[21] We recently used hAPP mice to determine the effect of high Aβ levels on neural network activity and the dependence of this effect on tau.

High Levels of Aβ Cause Epilepsy and Cognitive Deficits

The brain is characterized by multiple levels of complexity, ranging from molecules and individual synapses to circuits and interconnected networks. Activities in lower levels determine activities in higher levels and vice versa. Consequently, molecular and synaptic alterations can affect the function of networks and, in turn, alterations in network functions can affect individual synapses and molecules. It is well known that Aβ causes depression of excitatory neurotransmission at specific synaptic connections (Figure 1),[4, 8, 23–26] but the net effect of Aβ on the activity of microcircuits and broader neural networks had been unknown.

To shed light on this issue, we continually monitored neuronal activity in cortical and hippocampal networks by video electroencephalography (EEG) recordings in hAPP mice (J20 line; hAPPJ20), which have behavioral and synaptic deficits but no obvious neuronal loss.[4] These recordings revealed frequent epileptiform activity including spikes and sharp waves (Figure 1). The hAPPJ20 mice also had intermittent unprovoked seizures involving diverse regions of the neocortex and hippocampus that were not accompanied by tonic or clonic motor activity (Figure 1). These results suggest that high levels of Aβ are sufficient to elicit epileptiform activity in vivo in the absence of frank neurodegeneration. Therefore, aberrant network synchronization appears to be a primary effect of high Aβ levels rather than a secondary consequence of extensive neurodegeneration. Electroencephalographic epileptiform activity has subsequently been identified in independent transgenic mouse models of AD, including hAPPJ9/FYN mice (unpublished data), Tg2576 mice,[27] and hAPP/PS1 mice,[28] underlining the robustness of this Aβ effect.

Several lines of evidence suggest that Aβ-induced aberrant neuronal activity could contribute to cognitive deficits in hAPP mice and in AD. Epileptic activity triggers a variety of inhibitory compensatory responses in hippocampal circuits to counteract imbalances in network activity

(Figure 2).[4] Although these compensatory inhibitory mechanisms may dampen aberrant increases in network activity, they may also interfere with normal neuronal and synaptic functions required for learning and memory.[22] In hAPP mice, Aβ-induced epileptic activity was associated with sprouting of inhibitory axonal terminals in the molecular layer of the dentate gyrus, enhanced synaptic inhibition, and alterations in several calcium- and activity-regulated proteins in granule cells including calbindin, Fos, and Arc (Figure 2B).[4, 10, 12–14] Importantly, these alterations correlated tightly with each other and with deficits in learning and memory,[10] suggesting that Aβ-induced aberrant neuronal activity and associated compensatory inhibitory responses may be causally linked to cognitive decline (Figure 2A). We further assessed this possibility by crossing hAPP mice onto a tau-deficient (tau−/−) background, a genetic manipulation that blocks Aβ- and excitotoxin-induced overexcitation.[4–5] Reducing tau levels in hAPP mice prevented learning and memory deficits, compensatory inhibitory responses, premature mortality, and most evidence for aberrant network activity without affecting either hAPP or Aβ (Figure 3).[4–5] These results are consistent with our hypothesis that Aβ-induced aberrant neuronal activity contributes causally to learning and memory deficits in hAPP mice and possibly in AD.

The incidence of unprovoked seizures is clearly higher in sporadic AD than in reference populations, and the increase appears to be independent of disease stage.[2, 29–31] However, just as in hAPP mice, frank convulsive seizures are rather infrequent in AD. Nonetheless, 7% to 21% of patients with sporadic AD are estimated to have at least 1 unprovoked clinically apparent seizure during their illness.[2, 29–33] The relative risk of unprovoked seizures markedly increases in patients with early-onset AD, reaching 3-, 20-, and 87-fold with dementia onset when aged 70–79, 60–69, or 50–59 years, respectively.[2]

The relationship between clinically apparent seizures and AD is even stronger in autosomal dominant early-onset AD, which can be caused by mutations in hAPP (≥23 mutations), presenilin-1 (≥174 mutations), or presenilin-2 (≥14 mutations) and by duplications of wild-type hAPP (≥7 duplications).[34] These genetic alterations either increase Aβ42 production or the Aβ42:Aβ40 ratio or promote Aβ aggregation, providing strong evidence for a causal role of Aβ in AD. Notably, more than 30 mutations in presenilin-1 are associated with epilepsy,[35] and 56% of patients with early-onset AD with APP duplications have seizures.[3] Around 83% of pedigrees with very early onset of dementia (<40 years of age) show frank seizures or epilepsy.[1] Most cases of Down syndrome have an extra copy of the hAPP gene and develop early-onset AD; notably, 84% of those cases also have frank seizures.[36]

These clinical observations are consistent with our experimental findings and with our hypothesis that Aβ is an important cause of aberrant neural network synchronization in AD.

Apolipoprotein E4 is Associated with Subclinical Epileptiform Activity in Carriers without Dementia

Apolipoprotein is the most important known genetic risk factor for sporadic AD. Although the mechanisms underlying this link remain to be fully elucidated, much evidence suggests that ApoE4 contributes to AD pathogenesis through both Aβ-dependent and Aβ-independent pathways.[19] Aberrant increases in network excitability may represent a critical convergence point for the adverse effects of ApoE4 and Aβ in the pathogenesis of AD. In contrast to noncarriers, ApoE4 carriers without dementia showed signs of epileptiform activity and sharp waves on their EEGs after hyperventilation, although their EEGs were normal under resting conditions.[37] Similar changes have been found in subjects with high familial risk of developing AD, such as first-order relatives of patients with early-onset AD.[38] Apolipoprotein E4 also exacerbates epilepsy and promotes memory impairment in patients with long-standing intractable temporal lobe epilepsy.[39] These data indicate that major genetic risk factors for

developing AD are associated with increased network excitability in individuals without dementia, suggesting that this type of network dysfunction might play an early role in the establishment of pathogenic cascades leading to AD.

Amnestic Wandering and Disorientation in AD can be Associated with Epileptiform Activity

Many patients with AD experience fluctuations in cognitive functions such as transient episodes of amnestic wandering and disorientation.[22, 40] The intermittent inability to retrieve memories cannot be easily explained by relatively protracted processes such as neuronal loss, plaque deposition, or tangle formation. It seems more likely that abnormal neuronal network activity is to blame. Interestingly, amnestic episodes in patients with AD have been associated with epileptiform EEG discharges such as spikes and sharp waves.[41] What is more, these specific cognitive disturbances and the associated epileptiform EEG discharges could be prevented by antiepileptic treatment.[41] Epileptiform discharges in patients with temporal lobe epilepsy can also lead to transient amnesia and even simulate AD-like memory disturbances.[42] Therefore, nonconvulsive epileptiform activity could underlie at least some of the cognitive impairments observed in AD. Prospective clinical investigations focusing on hard-to-detect forms of epileptic activity are needed to further test this hypothesis in the clinic.

Therapeutic Implications

Many drugs for AD currently in clinical trials aim to reduce Aβ levels. However, the efficacy and long-term safety of these drugs have not yet been established. The studies discussed above suggest that reducing aberrant synchronization of neuronal activity may effectively protect the brain against Aβ's adverse effects on cognitive functions and thus could provide a complementary or alternative therapeutic strategy. We specifically hypothesize that cognitive deficits in hAPP mice, and perhaps in humans with AD, result from the combination of aberrant excitatory neuronal activity and of compensatory inhibitory responses that reduce overexcitation but end up constraining the functional agility of processes required for learning and memory (Figure 2A). Combination treatments may be required to block the contributions of overexcitation and overinhibition to AD-related cognitive deficits, although it seems reasonable to speculate that blocking the former should prevent, and might reverse, the latter.

Low doses of the {gamma}-aminobutyric acid A (GABAA) receptor antagonist picrotoxin prevented long-term potentiation deficits in the dentate gyrus and cognitive impairments in hAPP/presenilin 1 mice[43] as well as in Ts65Dn mice, a mouse model of Down syndrome.[44] These results indicate that inhibition in the dentate gyrus may critically contribute to cognitive impairments in these overlapping disorders. However, blocking inhibition with GABAA receptor antagonists can also exacerbate or precipitate seizures in hAPP mice,[4, 45] making this therapeutic intervention risky, at least as a monotherapy. Blocking overexcitation might provide a more effective upstream approach. A key question is whether any of the available Food and Drug administration–approved antiepileptic drugs could prevent or ameliorate Aβ-induced aberrant network excitation. Notably, some of the most commonly used antiepileptic drugs actually worsened seizure activity in hAPPJ20 mice,[46] underlining the need to carefully evaluate these agents at the preclinical level before designing clinical trials for people with AD or mild cognitive impairment. Consistent with this notion, the few clinical trials of antiepileptic drugs that have been conducted in AD so far have yielded disappointing results, but they were small and focused mostly on behavioral abnormalities in late stages of the disease.[47]

Up to one-third of patients with seizures without AD do not respond satisfactorily to medication and develop refractory epilepsy.[48] Antiepileptic drugs can also aggravate or precipitate certain types of seizures.[49] Thus, the efficacy of antiepileptic drugs in AD will likely depend on the

exact mechanisms of Aβ-induced dysrhythmias, which are currently unknown. Some antiepileptic drugs may elicit beneficial effects, whereas others may exacerbate aberrant network activity and cognitive decline. It is also possible that novel drugs may have to be developed to specifically block Aβ-induced dysrhythmias in AD. Our experimental data suggest that reducing tau levels is highly effective in preventing Aβ-induced network dysfunction and cognitive deficits in vivo (Figure 3).[4–5] However, much more research is needed to further assess the efficacy and safety of this novel therapeutic strategy.

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References

1. Snider BJ, Norton J, Coats MA, et al. Novel presenilin 1 mutation (S170F) causing Alzheimer disease with Lewy bodies in the third decade of life. Arch Neurol 2005;62(12):1821–1830. [PubMed: 16344340]
2. Amatniek JC, Hauser WA, DelCastillo-Castaneda C, et al. Incidence and predictors of seizures in patients with Alzheimer's disease. Epilepsia 2006;47(5):867–872. [PubMed: 16686651]
3. Cabrejo L, Guyant-Maréchal L, Laquerriére A, et al. Phenotype associated with APP duplication in five families. Brain 2006;129(pt 11):2966–2976. [PubMed: 16959815]
4. Palop JJ, Chin J, Roberson ED, et al. Aberrant excitatory neuronal activity and compensatory remodeling of inhibitory hippocampal circuits in mouse models of Alzheimer's disease. Neuron 2007;55(5):697–711. [PubMed: 17785178]
5. Roberson ED, Scearce-Levie K, Palop JJ, et al. Reducing endogenous tau ameliorates amyloid β-induced deficits in an Alzheimer's disease mouse model. Science 2007;316(5825):750–754. [PubMed: 17478722]
6. deIpolyi AR, Rankin KP, Mucke L, Miller BL, Gorno-Tempini ML. Spatial cognition and the human navigation network in AD and MCI. Neurology 2007;69(10):986–997. [PubMed: 17785667]
7. Deipolyi AR, Fang S, Palop JJ, Yu G-Q, Wang X, Mucke L. Altered navigational strategy use and visuospatial deficits in hAPP transgenic mice. Neurobiol Aging 2008;29(2):253–266. [PubMed: 17126954]
8. Hsia AY, Masliah E, McConlogue L, et al. Plaque-independent disruption of neural circuits in Alzheimer's disease mouse models. Proc Natl Acad Sci U S A 1999;96(6):3228–3233. [PubMed: 10077666]
9. Chapman PF, White GL, Jones MW, et al. Impaired synaptic plasticity and learning in aged amyloid precursor protein transgenic mice. Nat Neurosci 1999;2(3):271–276. [PubMed: 10195221]
10. Palop JJ, Jones B, Kekonius L, et al. Neuronal depletion of calcium-dependent proteins in the dentate gyrus is tightly linked to Alzheimer's disease-related cognitive deficits. Proc Natl Acad Sci U S A 2003;100(16):9572–9577. [PubMed: 12881482]
11. Kobayashi DT, Chen KS. Behavioral phenotypes of amyloid-based genetically modified mouse models of Alzheimer's disease. Genes Brain Behav 2005;4(3):173–196. [PubMed: 15810905]
12. Palop JJ, Chin J, Bien-Ly N, et al. Vulnerability of dentate granule cells to disruption of Arc expression in human amyloid precursor protein transgenic mice. J Neurosci 2005;25(42):9686–9693. [PubMed: 16237173]
13. Chin J, Palop JJ, Puoliväli J, et al. Fyn kinase induces synaptic and cognitive impairments in a transgenic mouse model of Alzheimer's disease. J Neurosci 2005;25(42):9694–9703. [PubMed: 16237174]
14. Cheng IH, Scearce-Levie K, Legleiter J, et al. Accelerating amyloid-β fibrillization reduces oligomer levels and functional deficits in Alzheimer disease mouse models. J Biol Chem 2007;282(33):23818–23828. [PubMed: 17548355]

15. Meilandt WJ, Yu G-Q, Chin J, et al. Enkephalin elevations contribute to neuronal and behavioral impairments in a transgenic mouse model of Alzheimer's disease. J Neurosci 2008;28(19):5007–5017. [PubMed: 18463254]
16. Janus C, Westaway D. Transgenic mouse models of Alzheimer's disease. Physiol Behav 2001;73(5):873–886. [PubMed: 11566220]
17. Götz J, Ittner LM. Animal models of Alzheimer's disease and frontotemporal dementia. Nat Rev Neurosci 2008;9(7):532–544. [PubMed: 18568014]
18. Wyss-Coray T, Masliah E, Mallory M, et al. Amyloidogenic role of cytokine TGF-β1 in transgenic mice and Alzheimer's disease. Nature 1997;389(6651):603–606. [PubMed: 9335500]
19. Mahley RW, Weisgraber KH, Huang Y. Apolipoprotein E4: a causative factor and therapeutic target in neuropathology, including Alzheimer's disease. Proc Natl Acad Sci U S A 2006;103(15):5644–5651. [PubMed: 16567625]
20. Lewis J, Dickson DW, Lin WL, et al. Enhanced neurofibrillary degeneration in transgenic mice expressing mutant tau and APP. Science 2001;293(5534):1487–1491. [PubMed: 11520987]
21. Masliah E, Rockenstein E, Veinbergs I, et al. β-Amyloid peptides enhance {alpha}-synuclein accumulation and neuronal deficits in a transgenic mouse model linking Alzheimer's disease and Parkinson's disease. Proc Natl Acad Sci U S A 2001;98(21):12245–12250. [PubMed: 11572944]
22. Palop JJ, Chin J, Mucke L. A network dysfunction perspective on neurodegenerative diseases. Nature 2006;443(7113):768–773. [PubMed: 17051202]
23. Walsh DM, Klyubin I, Fadeeva JV, et al. Naturally secreted oligomers of amyloid β protein potently inhibit hippocampal long-term potentiation in vivo. Nature 2002;416(6880):535–539. [PubMed: 11932745]
24. Kamenetz F, Tomita T, Hsieh H, et al. APP processing and synaptic function. Neuron 2003;37(6):925–937. [PubMed: 12670422]
25. Hsieh H, Boehm J, Sato C, et al. AMPAR removal underlies Aβ-induced synaptic depression and dendritic spine loss. Neuron 2006;52(5):831–843. [PubMed: 17145504]
26. Shankar GM, Bloodgood BL, Townsend M, Walsh DM, Selkoe DJ, Sabatini BL. Natural oligomers of the Alzheimer amyloid-β protein induce reversible synapse loss by modulating an NMDA-type glutamate receptor-dependent signaling pathway. J Neurosci 2007;27(11):2866–2875. [PubMed: 17360908]
27. Chin, J.; Ling, H-P.; Comery, T., et al. Chronic imbalance in neuronal activity and compensatory plasticity are associated with cognitive impairment in Tg2576 and PS1/APP mouse models of Alzheimer's disease. The International Conference on Alzheimer's Disease; Chicago, IL. July 27, 2008; 2008.
28. Tanila, J.; Minkeviciene, R.; Dobszay, MB., et al. Fibrillar beta-amyloid associates with epileptic seizures in APPswe/PS1de9 mice and changes excitability in cortical and hippocampal neurons. The Society for Neuroscience Annual Meeting; Washington, DC. Nov 18, 2008; 2008.
29. Hauser WA, Morris ML, Heston LL, Anderson VE. Seizures and myoclonus in patients with Alzheimer's disease. Neurology 1986;36(9):1226–1230. [PubMed: 3092131]
30. Romanelli MF, Morris JC, Ashkin K, Coben LA. Advanced Alzheimer's disease is a risk factor for late-onset seizures. Arch Neurol 1990;47(8):847–850. [PubMed: 2375689]
31. Mendez M, Lim G. Seizures in elderly patients with dementia: epidemiology and management. Drugs Aging 2003;20(11):791–803. [PubMed: 12964886]
32. Mendez MF, Catanzaro P, Doss RC, ARguello R, Frey WH II. Seizures in Alzheimer's disease: clinicopathologic study. J Geriatr Psychiatry Neurol 1994;7(4):230–233. [PubMed: 7826492]
33. Volicer L, Smith S, Volicer BJ. Effect of seizures on progression of dementia of the Alzheimer type. Dementia 1995;6(5):258–263. [PubMed: 8528372]
34. The Alzheimer disease and frontotemporal dementia mutation database. Flanders Interuniversity Institute for Biotechnology Department of Molecular Genetics Web site; 2008. http://www.molgen.ua.ac.be. Accessed September 6
35. Larner AJ, Doran M. Clinical phenotypic heterogeneity of Alzheimer's disease associated with mutations of the presenilin-1 gene. J Neurol 2006;253(2):139–158. [PubMed: 16267640]
36. Lai F, Williams RS. A prospective study of Alzheimer disease in Down syndrome. Arch Neurol 1989;46(8):849–853. [PubMed: 2527024]

37. Ponomareva NV, Korovaitseva GI, Rogaev EI. EEG alterations in non-demented individuals related to apolipoprotein E genotype and to risk of Alzheimer disease. Neurobiol Aging 2008;29(6):819–827. [PubMed: 17293007]
38. Ponomareva NV, Selesneva ND, Jarikov GA. EEG alterations in subjects at high familial risk for Alzheimer's disease. Neuropsychobiology 2003;48(3):152–159. [PubMed: 14586166]
39. Busch RM, Lineweaver TT, Naugle RI, et al. ApoE-epsilon4 is associated with reduced memory in long-standing intractable temporal lobe epilepsy. Neurology 2007;68(6):409–414. [PubMed: 17283313]
40. Bradshaw J, Saling M, Hopwood M, Anderson V, Brodtmann A. Fluctuating cognition in dementia with Lewy bodies and Alzheimer's disease is qualitatively distinct. J Neurol Neurosurg Psychiatry 2004;75(3):382–387. [PubMed: 14966152]
41. Rabinowicz AL, Starkstein SE, Leiguarda RC, Coleman AE. Transient epileptic amnesia in dementia: a treatable unrecognized cause of episodic amnestic wandering. Alzheimer Dis Assoc Disord 2000;14 (4):231–233. [PubMed: 11186602]
42. Sinforiani E, Manni R, Bernasconi L, Banchieri LM, Zucchella C. Memory disturbances and temporal lobe epilepsy simulating Alzheimer's disease: a case report. Funct Neurol 2003;18(1):39–41. [PubMed: 12760413]
43. Yoshiike Y, Kimura T, Yamashita S, et al. GABA(A) receptor-mediated acceleration of aging-associated memory decline in APP/PS1 mice and its pharmacological treatment by picrotoxin. PLoS ONE 2008;3(8):e3029. [PubMed: 18716656]
44. Fernandez F, Morishita W, Zuniga E, et al. Pharmacotherapy for cognitive impairment in a mouse model of Down syndrome. Nat Neurosci 2007;10(4):411–413. [PubMed: 17322876]
45. Del Vecchio RA, Gold LH, Novick SJ, Wong G, Hyde LA. Increased seizure threshold and severity in young transgenic CRND8 mice. Neurosci Lett 2004;367(2):164–167. [PubMed: 15331144]
46. Palop, JJ.; Thwin, MT.; Ho, K., et al. Alterations in voltage-gated sodium channels of transgenic mouse models of Alzheimer's disease: implications for Aβ-induced network dysfunction. The International Conference of Alzheimer's Disease; Chicago, IL. July 27, 2008; 2008.
47. Herrmann N, Lanctot KL, Rothenburg LS, Eryavec G. A placebo-controlled trial of valproate for agitation and aggression in Alzheimer's disease. Dement Geriatr Cogn Disord 2007;23(2):116–119. [PubMed: 17148938]
48. French JA. Refractory epilepsy: clinical overview. Epilepsia 2007;48(suppl 1):3–7. [PubMed: 17316406]
49. Thomas P, Valton L, Genton P. Absence and myoclonic status epilepticus precipitated by antiepileptic drugs in idiopathic generalized epilepsy. Brain 2006;129(Pt 5):1281–1292. [PubMed: 16513683]

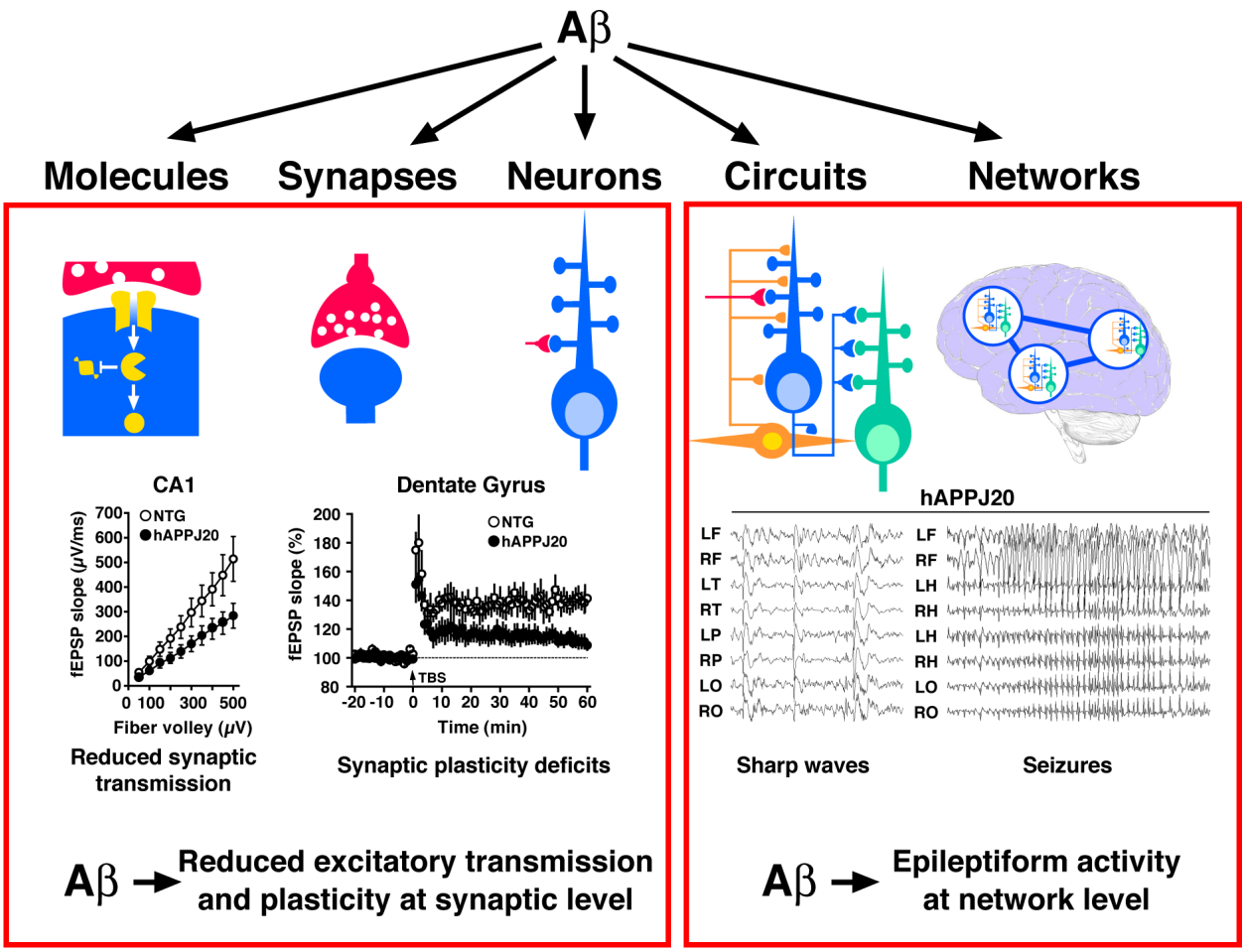

Figure 1. βAmyloid (Aβ) can affect neuronal activity at multiple levels of complexity

High levels of Aβ depress excitatory synaptic transmission and impair synaptic plasticity at the level of specific synapses (A) but elicit epileptiform activity and seizures at the network level (B). Whether there is a causal relationship between these Aβ effects is unknown. F indicates frontal; fEPSP, field excitatory postsynaptic potentials; H, hippocampal; hAPPJ20, human amyloid precursor protein transgenic mice; L, left; NTG, nontransgenic mice; O, posterior-parietal; P, parietal; R, right; T, temporal; and TBS, {theta}-burst stimulation. Adapted from Neuron[4] and Nature.[22]

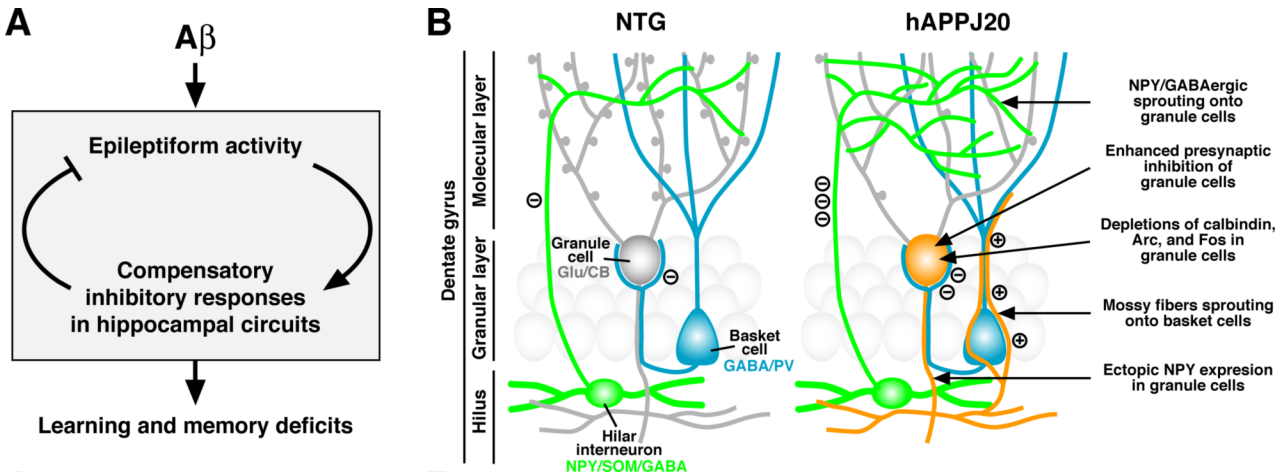

Figure 2. Our latest view of the β-amyloid (Aβ) cascade hypothesis and resultant hippocampal remodeling

A, High levels of Aβ induce epileptiform activity, which triggers compensatory inhibitory responses to counteract overexcitation. Both aberrant excitatory neuronal activity and compensatory inhibitory responses may contribute to Alzheimer disease–related cognitive deficits. B, Aβ-dependent circuit remodeling in the dentate gyrus of human amyloid precursor protein transgenic mice (hAPPJ20). In contrast to nontransgenic mice (NTG), hAPPJ20 mice show increased sprouting of inhibitory axonal terminals in the molecular layer, enhanced synaptic inhibition, ectopic neuropeptide Y (NPY) expression in granule cells, and depletion of activity-dependent proteins such as calbindin, Arc, and Fos. These alterations likely reflect compensatory inhibitory responses to aberrant excitatory neuronal activity. CB indicates calbindin; GABA, {gamma}-aminobutyric acid; Glu, glutamate; PV, parvalbumin; and SOM, somatostatin. Adapted from Neuron.[4]

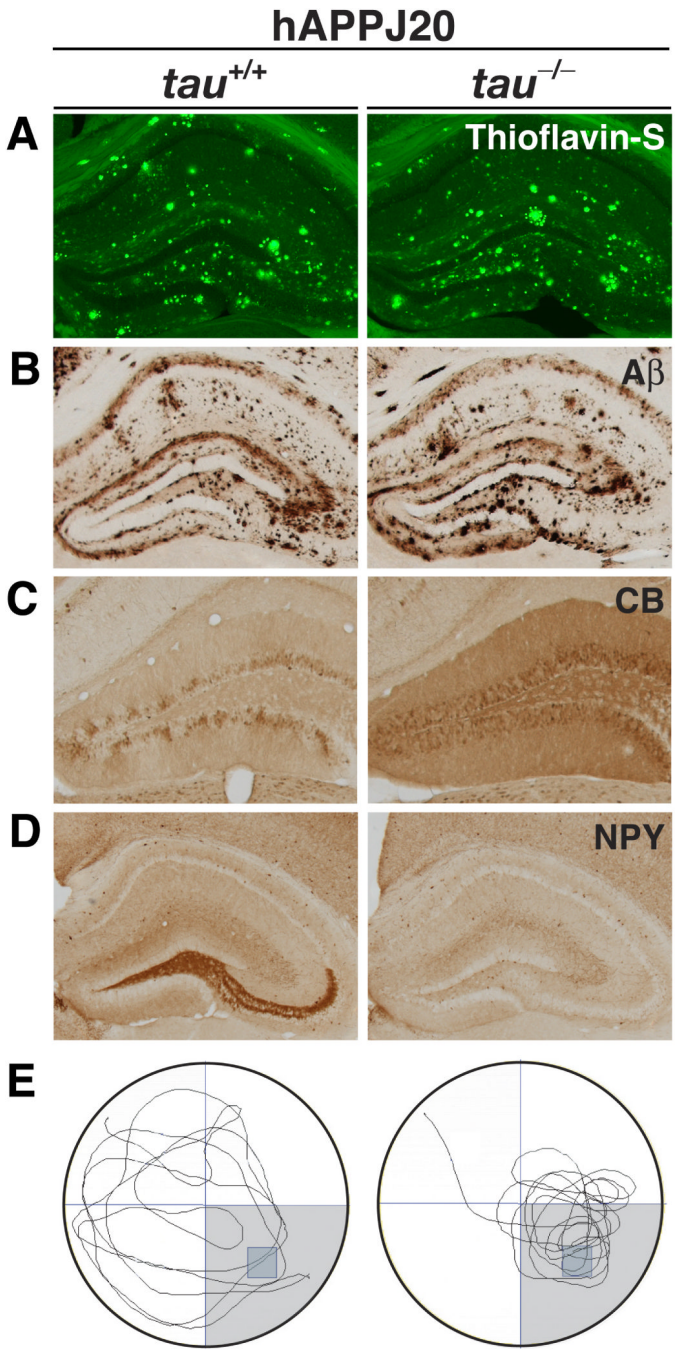

Figure 3. Tau reduction prevents β-amyloid (Aβ) toxicity in vivo

Thioflavin-S staining (A) and anti-Aβ immunostaining (B) of hippocampal amyloid plaques in mice with human amyloid precursor protein transgenic mice (hAPPJ20) with 2 (tau+/+) or no (tau−/−) functional tau alleles revealed that tau reduction did not alter plaque loads in hAPP mice. However, tau reduction effectively prevented Aβ-induced depletion of calbindin (CB) (C) and increases in neuropeptide Y (NPY) (D) in the dentate gyrus as well as spatial memory deficits in the Morris water maze (E). The representative path tracings in (E) were obtained in a probe trial (platform removed) 24 hours after 3 days of hidden platform training. Tau reduction markedly increased focused search activity in the target quadrant (light gray) and

over the platform location (dark gray), suggesting improved spatial memory retention. Adapted from Neuron[4] and Science.[5]