Journal of Alzheimer's Disease 47 (2015) 149–156
DOI 10.3233/JAD-150381
IOS Press

Commentary

Treatment of Alzheimer's Disease: The Legacy of the Cholinergic Hypothesis, Neuroplasticity, and Future Directions

J. Wesson Ashford*
Stanford/VA Aging Clinical Research and Alzheimer Centers, VA Palo Alto Health Care System and Stanford University, Stanford, CA, USA

Accepted 18 May 2015

Abstract. In this issue, an article by Waring et al. provides a meta-analysis of the effects of apo-lipo-protein E (APOE) genotype on the beneficial effect of acetyl-cholinesterase inhibitors (AChEIs) in patients with Alzheimer's disease (AD). There was no significant effect found. As of 2015, AChEI medications are the mainstay of AD treatment, and APOE genotype is the most significant factor associated with AD causation. This lack of a significant effect of APOE is analyzed with respect to the "Cholinergic Hypothesis" of AD, dating from 1976, through the recognition that cholinergic neurons are not the sole target of AD, but rather that AD attacks all levels of neuroplasticity in the brain, an idea originated by Ashford and Jarvik in 1985 and which still provides the clearest explanation for AD dementia. The "Amyloid Hypothesis" is dissected back to the alpha/beta pathway switching mechanism affecting the nexin-amyloid pre-protein (NAPP switch). The NAPP switch may be the critical neuroplasticity component of all learning involving synapse remodeling and subserve all learning mechanisms. The gamma-secretase cleavage is discussed, and its normal complementary products, beta-amyloid and the NAPP intracellular domain (NAICD), appear to be involved in natural synapse removal, but the link to AD dementia may involve the NAICD rather than beta-amyloid. Understanding neuroplasticity and the critical pathways to AD dementia are needed to determine therapies and preventive strategies for AD. In particular, the effect of APOE on AD predisposition needs to be established and a means found to adjust its effect to prevent AD.

Keywords: Alzheimer disease, cholinesterase inhibitors, ApoE, acetylcholine, neuronal plasticity, MAPT protein, human amyloid beta-protein, leptin

As of 2015, the main therapy for Alzheimer's disease (AD) is treatment with an acetyl-cholinesterase inhibitor (AChEI), with four drugs approved by the FDA for this purpose: tacrine, donepezil, galantamine, and rivastigmine [1]. Only one other drug, memantine, is approved by the FDA for AD treatment, and it is usually used as a supplement to an AChEI. Currently, the major factor associated with AD causation, including age of onset, is the apolipoprotein E (APOE) genotype [2–4]. A persistent question regarding the treatment of AD has been whether specific APOE genotypes might influence the therapeutic efficacy of any intervention. Many studies of therapeutic agents have sought to stratify samples according to APOE genotype, with relatively little clear determination that APOE genotype has a substantial effect on therapeutic benefit in AD patients. An article in this issue by Waring et al. [5] provides an important analysis of the relationship between APOE genotype and AChEI benefit across three studies of placebo versus donepezil, with 170 of

*Correspondence to: J. Wesson Ashford, MD, PhD, Director, War Related Illness & Injury Study Center - 151-Y, VA Palo Alto Health Care System, 3801 Miranda Avenue, Palo Alto, CA 94304, USA. Office: +1 650 493 5000 11 64059; Secretary: +1 650 852 3316; Fax: +1 650 852 3297; Cell: +1 415 722 0187; E-mail: ashford @stanford.edu.

ISSN 1387-2877/15/$35.00

the placebo subjects and 165 of the donepezil subjects having APOE ε4 genotype available. The conclusion is that there is no significant relationship between APOE genotype and medication response. The findings do not prove that there is absolutely no interaction, but the magnitude of an effect, if it exists, is too small or too variable to be detected by the methodologies used. This negative finding is important for considering the precise roles APOE genotype and AD pathology have in leading to dementia and what point in the AD process therapy should target.

The "cholinergic hypothesis" of AD [6] began with findings of decrease of the enzyme choline acetyltransferase in AD patients by three labs in the United Kingdom in 1976 [7–9]. These findings led to the first test of the AChEI treatment of AD patients in a double-blind study in 1981 [10] and a demonstration of enhanced memory in this patient population in 1982 [11]. There was also a demonstration that the cholinergic neurons most affected in AD originated in the nucleus basalis of Meynert [12] and that there was a relationship between loss of cholinergic innervation and amyloid deposition in neuritic plaques [13]. Based on the cholinergic dysfunction and preliminary therapeutic findings, AChEI medications were tested and then found to benefit AD patients clinically, leading to the first FDA approval of a medication for AD, tacrine, in 1993 [14]. Of many cholinergic therapies, only the AChEI approach has shown consistent benefit, though that benefit has been considered "modest" [15, 16], setting the AD clock back less than 6 months [17]. However, AChEI treatment slows the progression of hippocampal atrophy, suggesting that this class of drug has a neuroprotective effect against AD pathology [18, 19].

In spite of the strength of the cholinergic hypothesis, it was apparent that AD was much more than a disease simply attacking cholinergic neurons. Additionally, monaminergic neurons are attacked early in the disease process [20], including noradrenergic neurons [21, 22], serotonergic neurons [23], and neurons with NMDA glutamatergic receptors [24]. Further, AD has a specific pattern of attacking the cerebral cortex [25], which also has a temporal order to its progression [26]. At all levels, neuropathology, psychopathology, and disruption of social function, AD pathology affects systems related to the formation of new memory [27]. Accordingly, AD pathology must be a process attacking the fundamental neuroplasticity mechanisms of the brain [10, 28, 29].

When the major protein associated with the neuritic plaques was identified as amyloid-β (Aβ) [30] and numerous young-onset AD genes were associated with amyloid production and metabolism, the "amyloid hypothesis" was invoked to explain AD [31–33]. However, this hypothesis has failed to provide an explanation for the full range of AD pathology or lead to any benefit for AD patients, with most studies showing substantial harm in treating the amyloid depositions associated with AD [34–38]. Fatal problems for the amyloid hypothesis have been that Aβ is a highly turned-over normal protein in the brain [39], and Aβ levels decline in the cerebrospinal fluid (CSF) in association with APOE genotype, not tau pathology [40], nor CSF tau levels, nor dementia [41, 42]. Further, Aβ levels in the brain do not predict the age at onset, disease duration, or dementia severity [43]. Also, neuritic plaques have a poor relationship with the density and distribution of tau pathology [44]. The amyloid hypothesis describes a role for Aβ in causing AD, but does not explain the normal role of Aβ, which is highly conserved evolutionarily, or how that normal role is related to the vulnerability to AD pathology. Importantly, the amyloid hypothesis has not provided a link to the disorder of neuroplasticity central to AD [45].

The association between APOE and AD is the strongest genetic risk factor in medicine [46]. With approximately 50% of AD causation attributable to the APOE ε4 allele and considerable protection with APOE ε2, the APOE genotype can be considered to explain 90% of AD [47]. One of the most important unresolved issues in AD study is the specific role of the APOE molecule [48, 49], including its evolution, its normal action relevant to neuroplasticity and AD, and how that action is differentially affected by the three common alleles—ε2, ε3, and ε4, leading to a substantial increase of AD risk associated with the ε4 and a decrease associated with the ε2. While APOE has a major role in chaperoning lipids, particularly cholesterol, it also has a role in Aβ processing [50–52]. It has been recently established that APOE genotype influences the Aβ levels in the CSF and brain [40–42], though both biomarkers are unrelated to the development of dementia.

Another issue is whether there is any influence of APOE on the rate of decline in AD patients once dementia has developed. The article by Waring et al. in this issue [5] notes that a positive APOE ε4 allele status is associated with greater magnitude of cognitive change in placebo-treated patients compared with patients without an APOE ε4 allele. Consequently, during the time of most measurable progression, the APOE protein appears to have some impact on the placebo

effect. As noted in the article, this effect could be related to test-retest practice effects of the instrument used in the studies, the ADAS-Cog, possibly related to the subjects with the APOE ε4 allele having more severe underlying deficits of learning. However, generally, there is no indication that the APOE protein has any impact on the progression of dementia once it has begun or the rate of development of the AD pathology. As a genetic factor, APOE appears to play a major role in predisposing to AD through a prodromal effect related to Aβ [53, 54], an effect that presumably begins well before birth when APOE is first being synthesized in the brain. But there appears to be little direct effect of APOE genotype on the progression of dementia once the mild cognitive impairment phase has developed [42]. In spite of extensive study, no treatment related to the APOE factor has yet been developed either to prevent AD or to slow the progression of dementia [55].

The finding that APOE genotype has no significant effect on AChEI treatment is consistent with the perspective that the effect of APOE has a long-term impact on the development of Aβ pathology [56], but that APOE has no specific or significant effect on dementia, its progression, or its treatment. Also relevant is the perspective that there are multiple pathological manifestations in AD with various temporal relationships to age, but no clear cause-and-effect relationships with each other [57]. Each AD-related process presumably has its own biological basis which suffers an increased failure rate with aging described by survival dynamics [58], similar to the aging effect on dementia development associated with APOE genotype [47]. More accurate measurements of the severity of the AD manifestations and defining their precise courses indexed to the temporal progression of dementia would be of great help for defining AD and determining the benefits of treatment [59–61]. Here, the results of the Waring et al. [5] analysis establish an important point for distinguishing where different causal and therapeutic factors may be affecting AD.

Given the long-term use of AChEI therapy, further understanding of this therapy is warranted. A recent study has pointed out the different effects of the various AChEI agents on brain cholinergic function [62, 63]. Specifically, some agents induce increased levels of AChE, while others do not. Further, the long-term benefits of the various AChEI agents appear to be different [64–66], with galantamine having a longer duration of benefit than donepezil [67, 68]. The rapid deterioration associated with the termination of donepezil treatment has been attributed to the underlying progression of the disease [15], but a more likely explanation is that the AChEIs actually slow the disease process slightly while the elevated levels of AChE, induced by the AChEI treatment, trigger an anti-cholinergic crisis when AChEI agents are removed, leading to an increase rate of AD pathological damage which is not reversible on restarting the medication. However, the benefit of starting a treatment seems to occur regardless of prior treatment [69]. The study of Waring et al. emphasizes the importance of determining whether there are factors which influence medication efficacy for AD patients.

While the amyloid hypothesis and APOE genotype have failed to provide an AD therapy, the solid foundations of these factors should be examined for how they relate to the therapeutically relevant cholinergic hypothesis, other neurotransmitter dysfunctions, and the distinct anatomical neuropathological distribution of AD, particularly with regard to the central issue of neuroplasticity. The first aspect of the amyloid hypothesis that needs to be emphasized is the role of the amyloid pre-protein itself. To understand its role, this protein should be referred to as the "nexin-amyloid pre-protein" (NAPP), because this pre-protein is catabolized by two equally important enzymes, an α-secretase and a β-secretase. The α-secretase has two relevant variations, ADAM-10 and ADAM-17 [70–72], and leads to the formation of the nexin protein and the creation of new synapses. However, most research has been done on the β-secretase action, whose transmembrane product is cleaved by a γ-secretase, resulting in the formation of Aβ and the NAPP-intracellular domain (NAICD). Note that for every Aβ molecule produced, an NAICD molecule is produced. Both Aβ and NAICD are toxic to synapses and are likely involved in their routine removal, as is appropriate. Actually, the animal data suggesting a relationship between Aβ and AD may be an artefact of this natural synaptoxicity, not an indication that Aβ has any role in the cascade leading to dementia. The decision of whether the NAPP will pass down the α or β pathway (the NAPP-switch) is the critical neuroplasticity decision at all activated synapses involved in the formation of a new memory [42, 48, 73, 74]. Since synapses have relatively short half-lives, the creation and removal of synapses is a major normal activity of the brain (the human brain builds and demolishes trillions of synapses in every 24-h period). However, the absolute number of synapses actually decreases over time, as decades of life pass; thus there must be a slight imbalance towards a tendency for the NAPP switch to follow the β pathway. This tendency for increased β

processing of NAPP with aging may be creating a vulnerable target for AD pathology and could be the major factor leading to dementia, the "retrogenesis" of neurons, and cognitive dysfunction [75]. And early on in the development of AD-related dementia, there is an increase of neuroplastic activity [76], which is likely accelerating the AD pathological process as described here.

Of considerable importance at the NAPP switch, the control point of NAPP metabolism, is that acetylcholine, norepinephrine, and serotonin, all neurotransmitters with key roles in learning and memory [77, 78] and each disrupted by AD, all have critical roles in activating the α-secretase [70–72]. The common mechanism related to neuroplasticity, as it pertains to AD, is likely to be neurotransmitter signaling (involving calcium and a complex cascade of other cell proteins) modulating protein kinase C (PKC). PKC plays roles in activating the α-secretase cleavage of NAPP and blocking the phosphorylation of tau [79–82], actions which lead to the remodeling of synapses, thus serving the basis of formation of new memory substrates [83–86]. The effect of various neurotransmitters on PKC leading to control of the NAPP switch could be the unifying principle of neuroplasticity, subserving all types of learning and detail memory formation [87]. Since PKC is disrupted in AD [88], it is in a key position to be the protein mediating the several disparate factors which lead to AD pathology.

When α-secretase is not activated, the NAPP enters the default β pathway, to be cleaved by the β-secretase. The trans-membrane fragment is further cleaved by the γ-secretase to produce Aβ and NAICD [89]. The Aβ and NAICD products are destructive to synapses, presumably having the critical normal role of pruning those synapses no longer germane to the specific neurocognitive analysis being modified. Under normal circumstances, Aβ may be acting with the metabotropic glutamate receptor 5 to activate Fyn, which will in turn phosphorylate tau [90], and the NAICD is released inside the synapse and appears to have a specific role in gene expression and phosphorylating tau [74, 91, 92]. The NAICD may have a specific normal role to cause retraction of the synaptic machinery. However, under pathological circumstances the γ-secretase product Aβ is incorporated into neuritic plaques. Neuritic plaques themselves have not been shown to have a role in causing cognitive dysfunction in humans. During pathological circumstances, the production of the NAICD is essential for behavior deficits to develop in transgenic mice [93]. A potentially important note at this juncture is that the $A\beta_{42}$ is thought to be more related to pathological changes than the $A\beta_{40}$. However, the complementary NAICD of $A\beta_{42}$, NAICD-42, may represent the actual next pathological factor in the progression of the AD process leading to dementia. The production of the pathological NAICD likely triggers the hyperphosphorylation of tau [94], which leads to the formation of paired-helical filaments and then neuropil threads, which are the neurites defining the pathological senile plaques. As the neuropil threads are transported retrogradely in neuronal processes, they clog those processes, leading to massive amputation of axonal and dendritic trees, with clearly consequent loss of neuronal processes [95] and dementia. It is this tauopathic damage of neuronal processes which provides the clearest explanation for the extensive synapse loss of AD. Presumably the neurofibrillary tangles result from the retrograde transport of the neuropil threads all the way back to the cell body, leading to eventual cell death due to neurofibrillary congestion, but it is unlikely that the neurofibrillary tangles or cell death are the direct cause of the synapse loss or the AD dementia. And it is synapse loss which is most closely related to memory decline and dementia in AD [96, 97]. The loss of neuronal process trees would lead to large-scale release of tau protein into the extracellular space and also explain the elevation of tau in the CSF in relation to dementia [42].

Regarding the other FDA approved drug for AD, the locus of the beneficial action of memantine is the stabilization of the NMDA receptor, which has a central role in neuroplasticity, particularly in the branching of neural processes [98]. Stabilization of this receptor is clinically beneficial, at least in moderate to severely demented patients with AD. There is also evidence that memantine may extend the life-expectancy of AD patients to near normal [99].

There are numerous other agents which may positively or protectively modulate the AD pathological cascade, and many drugs are mentioned in articles cited in this commentary. Enhancement of several neurotransmitter systems may potentially lead to a long-term augmentation of α-secretase activity and reduction of β-secretase activity [20]. Monaminergic systems ascending from the brainstem can already be manipulated, for example, with the currently available drug formoterol [100]. However, so far, experimental treatments of these systems have not yet led to an AD treatment. The adipocyte-derived leptin, a pleiotropic hormone, decreases Aβ production and tau phosphorylation [101], representing another potential therapeutic avenue. There remains interest in whether certain NSAIDs can selectively modify the cleavage of the

γ-secretase to decrease $A\beta_{42}$ production [102] and prevent AD [103]. Inhibition of Fyn, a kinase which can phosphorylate tau, could potentially be blocked by saracatinib [104, 105]. It has also been long known that lithium and valproic acid can inhibitor glycogen-synthase-kinase 3β, which can phosphorylate tau, but there has been no evidence that these medications affect AD progression. Further, there are numerous agents which may be used in combination to slow or prevent the AD process [106]. With a broader understanding of the cascade of AD pathology, there are numerous points of potential intervention in the AD pathogenic pathway [107].

The major missing contribution for developing AD prevention strategies is an adjustment for APOE phenotype to prevent the prodromal changes of AD which lead to dementia [55]. Investigations of APOE would be great facilitated by acceptance of clinical APOE genotyping.

As of 2015, the only established interventions which affect AD pathology are the augmentation of cholinergic activity with AChEIs and stabilization of the NMDA effector mechanism with memantine. However, attention to how each step of the pathological pathways is affected by APOE and other causal factors will hopefully lead to the development of programs, probably beginning at birth or before, which will prevent the entire AD pathological process.

DISCLOSURE STATEMENT

Authors' disclosures available online (http://j-alz.com/manuscript-disclosures/15-0381r1).

REFERENCES

[1] Zemek F, Drtinova L, Nepovimova E, Sepsova V, Korabecny J, Klimes J, Kuca K (2014) Outcomes of Alzheimer's disease therapy with acetylcholinesterase inhibitors and memantine. *Expert Opin Drug Saf* **13**, 759-774.

[2] Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, Roses AD, Haines JL, Pericak-Vance MA (1993) Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* **261**, 921-923.

[3] Roses AD (1996) Apolipoprotein E alleles as risk factors in Alzheimer's disease. *Annu Rev Med* **47**, 387-400.

[4] Ashford JW (2004) APOE genotype effects on Alzheimer's disease onset and epidemiology. *J Mol Neurosci* **23**, 157-165.

[5] Waring JF, Tang Q, Robieson WZ, King DP, Das U, Dubow J, Dutta S, Marek GJ, Gault LM (2015) APOE-ε4 carrier status and donepezil response in patients with Alzheimer's disease. *J Alzheimers Dis* **47**, 137-148.

[6] Coyle JT, Price DL, DeLong MR (1983) Alzheimer's disease: A disorder of cortical cholinergic innervation. *Science* **219**, 1184-1190.

[7] Davies P, Maloney AJ (1976) Selective loss of central cholinergic neurons in Alzheimer's disease. *Lance* **2**, 1403.

[8] Bowen DM, Smith CB, White P, Davison AN (1976) Neurotransmitter-related enzymes and indices of hypoxia in senile dementia and other abiotrophies. *Brain* **99**, 459-496.

[9] Perry EK, Perry RH, Blessed G, Tomlinson BE (1977) Necropsy evidence of central cholinergic deficits in senile dementia. *Lancet* **1**, 189.

[10] Ashford JW, Jarvik L (1985) Alzheimer's disease: Does neuron plasticity predispose to axonal neurofibrillary degeneration? *N Engl J Med* **313**, 388-389.

[11] Davis KL, Mohs RC (1982) Enhancement of memory processes in Alzheimer's disease with multiple-dose intravenous physostigmine. *Am J Psychiatry* **139**, 1421-1424.

[12] Whitehouse PJ, Price DL, Clark AW, Coyle JT, DeLong MR (1981) Alzheimer disease: Evidence for selective loss of cholinergic neurons in the nucleus basalis. *Ann Neurol* **10**, 122-126.

[13] Struble RG, Cork LC, Whitehouse PJ, Price DL (1982) Cholinergic innervation in neuritic plaques. *Science* **216**, 413-415.

[14] Waldholz M (1993) FDA approves sale of Cognex for Alzheimer's: Warner-Lambert drug is sole treatment, could produce huge revenue. *Wall St J (East Ed)* **85**.

[15] Di Santo SG, Prinelli F, Adorni F, Caltagirone C, Musicco M (2013) A meta-analysis of the efficacy of donepezil, rivastigmine, galantamine, and memantine in relation to severity of Alzheimer's disease. *J Alzheimers Dis* **35**, 349-361.

[16] Tinklenberg JR, Kraemer HC, Yaffe K, O'Hara R, Ringman JM, Ashford JW, Yesavage JA, Taylor JL (2015) Donepezil treatment in ethnically diverse patients with Alzheimer disease. *Am J Geriatr Psychiatry* **23**, 384-390.

[17] Ashford JW, Schmitt FA, Wermeling D, Bieber F, Orazem J, Gulanski B (1996) Advantages of the "Time-Index" method for measurement of Alzheimer dementia: Assessment of metrifonate benefit. In *Alzheimer Disease: From Molecular Biology to Therapy*, Becker R, Giacobini E, eds. Birkhauser, Boston, pp. 431-434.

[18] Mori E, Hashimoto M, Krishnan KR, Doraiswamy PM (2006) What constitutes clinical evidence for neuroprotection in Alzheimer disease: Support for the cholinesterase inhibitors? *Alzheimer Dis Assoc Disord* **20**, S19-S26.

[19] Dubois B, Chupin M, Hampel H, Lista S, Cavedo E, Croisile B, Tisserand GL, Touchon J, Bonafe A, Ousset PJ, Ait Ameur A, Rouaud O, Ricolfi F, Vighetto A, Pasquier F, Delmaire C, Ceccaldi M, Girard N, Dufouil C, Lehericy S, Tonelli I, Duveau F, Colliot O, Garnero L, Sarazin M, Dormont D (2015) Donepezil decreases annual rate of hippocampal atrophy in suspected prodromal Alzheimer's disease. *Alzheimers Dement* (Epub, ahead of print) - Jan. 14, 2015 - pii: S1552-5260, pages 1-9.

[20] Trillo L, Das D, Hsieh W, Medina B, Moghadam S, Lin B, Dang V, Sanchez MM, De Miguel Z, Ashford JW, Salehi A (2013) Ascending monoaminergic systems alterations in Alzheimer's disease. Translating basic science into clinical care. *Neurosci Biobehav Rev* **37**, 1363-1379.

[21] Bondareff W, Mountjoy CQ, Roth M (1981) Selective loss of neurones of origin of adrenergic projection to cerebral cortex (nucleus locus coeruleus) in senile dementia. *Lancet* **1**, 783-784.

[22] Braak H, Del Tredici K (2011) The pathological process underlying Alzheimer's disease in individuals under thirty. *Acta Neuropathol* **121**, 171-181.

[23] Grinberg LT, Rub U, Ferretti RE, Nitrini R, Farfel JM, Polichiso L, Gierga K, Jacob-Filho W, Heinsen H (2009) The dorsal raphe nucleus shows phospho-tau neurofibrillary changes before the transentorhinal region in Alzheimer's disease. A precocious onset? *Neuropathol Appl Neurobiol* **35**, 406-416.

[24] Geddes JW, Chang-Chui H, Cooper SM, Lott IT, Cotman CW (1986) Density and distribution of NMDA receptors in the human hippocampus in Alzheimer's disease. *Brain Res* **399**, 156-161.

[25] Brun A, Englund E (1981) Regional pattern of degeneration in Alzheimer's disease: Neuronal loss and histopathological grading. *Histopathology* **5**, 549-564.

[26] Braak H, Braak E (1991) Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathol* **82**, 239-259.

[27] Ashford JW, Schmitt F, Kumar V (1998) Diagnosis of Alzheimer's disease. In *Advances in the Diagnosis and Treatment of Alzheimer's Disease*, Kumar V, Eisdorfer C, eds, Springer Publishing Company, New York.

[28] Ashford JW, Mattson M, Kumar V (1998) Neurobiological systems disrupted by Alzheimer's disease and molecular biological theories of vulnerability. In *Advances in the Diagnosis and Treatment of Alzheimer's Disease*, Kumar V, Eisdorfer C, eds, Springer Publishing Company, New York.

[29] Teter B, Ashford JW (2002) Neuroplasticity in Alzheimer's disease. *J Neurosci Res* **70**, 402-437.

[30] Wong CW, Quaranta V, Glenner GG (1985) Neuritic plaques and cerebrovascular amyloid in Alzheimer disease are antigenically related. *Proc Natl Acad Sci U S A* **82**, 8729-8732.

[31] Hardy J, Allsop D (1991) Amyloid deposition as the central event in the aetiology of Alzheimer's disease. *Trends Pharmacol Sci* **12**, 383-388.

[32] Hardy J, Selkoe DJ (2002) The amyloid hypothesis of Alzheimer's disease: Progress and problems on the road to therapeutics. *Science* **297**, 353-356.

[33] Selkoe DJ (1991) The molecular pathology of Alzheimer's disease. *Neuron* **6**, 487-498.

[34] Leissring MA (2014) Abeta degradation-the inside story. *Front Aging Neurosci* **6**, 229.

[35] Castellani RJ, Perry G (2012) Pathogenesis and disease-modifying therapy in Alzheimer's disease: The flat line of progress. *Arch Med Res* **43**, 694-698.

[36] Nalivaeva NN, Turner AJ (2013) The amyloid precursor protein: A biochemical enigma in brain development, function and disease. *FEBS Lett* **587**, 2046-2054.

[37] Drachman DA (2014) The amyloid hypothesis, time to move on: Amyloid is the downstream result, not cause, of Alzheimer's disease. *Alzheimers Dement* **10**, 372-380.

[38] Armstrong RA (2014) A critical analysis of the 'amyloid cascade hypothesis'. *Folia Neuropathol* **52**, 211-225.

[39] Bateman RJ, Munsell LY, Morris JC, Swarm R, Yarasheski KE, Holtzman DM (2006) Human amyloid-beta synthesis and clearance rates as measured in cerebrospinal fluid *in vivo*. *Nat Med* **12**, 856-861.

[40] Morris JC, Roe CM, Xiong C, Fagan AM, Goate AM, Holtzman DM, Mintun MA (2010) APOE predicts amyloid-beta but not tau Alzheimer pathology in cognitively normal aging. *Ann Neurol* **67**, 122-131.

[41] Kim S, Swaminathan S, Shen L, Risacher SL, Nho K, Foroud T, Shaw LM, Trojanowski JQ, Potkin SG, Huentelman MJ, Craig DW, DeChairo BM, Aisen PS, Petersen RC, Weiner MW, Saykin AJ (2011) Genome-wide association study of CSF biomarkers Abeta1-42, t-tau, and p-tau181p in the ADNI cohort. *Neurology* **76**, 69-79.

[42] Ashford JW, Salehi A, Furst A, Bayley P, Frisoni GB, Jack CR Jr, Sabri O, Adamson MM, Coburn KL, Olichney J, Schuff N, Spielman D, Edland SD, Black S, Rosen A, Kennedy D, Weiner M, Perry G (2011) Imaging the Alzheimer brain. *J Alzheimers Dis* **26**(Suppl 3), 1-27.

[43] Murray ME, Lowe VJ, Graff-Radford NR, Liesinger AM, Cannon A, Przybelski SA, Rawal B, Parisi JE, Petersen RC, Kantarci K, Ross OA, Duara R, Knopman DS, Jack CR Jr, Dickson DW (2015) Clinicopathologic and 11C-Pittsburgh compound B implications of Thal amyloid phase across the Alzheimer's disease spectrum. *Brain* **138**, 1370-1381.

[44] Geddes JW, Tekirian TL, Soultanian NS, Ashford JW, Davis DG, Markesbery WR (1997) Comparison of neuropathologic criteria for the diagnosis of Alzheimer's disease. *Neurobiol Aging* **18**, S99-S105.

[45] Sheng M, Sabatini BL, Sudhof TC (2012) Synapses and Alzheimer's disease. *Cold Spring Harb Perspect Biol* **4**, pii: 005777, pages 1-18.

[46] Serrano-Pozo A, Qian J, Monsell SE, Betensky RA, Hyman BT (2015) APOEepsilon2 is associated with milder clinical and pathological Alzheimer's disease. *Ann Neurol* (Epub ahead of print) Jan. 26, 2015, pages 1-47.

[47] Raber J, Huang Y, Ashford JW (2004) ApoE genotype accounts for the vast majority of AD risk and AD pathology. *Neurobiol Aging* **25**, 641-650.

[48] Glass DJ, Arnold SE (2012) Some evolutionary perspectives on Alzheimer's disease pathogenesis and pathology. *Alzheimers Dement* **8**, 343-351.

[49] Spinney L (2014) Alzheimer's disease: The forgetting gene. *Nature* **510**, 26-28.

[50] Kim J, Jiang H, Park S, Eltorai AE, Stewart FR, Yoon H, Basak JM, Finn MB, Holtzman DM (2011) Haploinsufficiency of human APOE reduces amyloid deposition in a mouse model of amyloid-beta amyloidosis. *J Neurosci* **31**, 18007-18012.

[51] Handattu SP, Monroe CE, Nayyar G, Palgunachari MN, Kadish I, van Groen T, Anantharamaiah GM, Garber DW (2013) *In vivo* and *in vitro* effects of an apolipoprotein e mimetic peptide on amyloid-beta pathology. *J Alzheimers Dis* **36**, 335-347.

[52] Kanekiyo T, Xu H, Bu G (2014) ApoE and Abeta in Alzheimer's disease: Accidental encounters or partners? *Neuron* **81**, 740-754.

[53] Mungas D, Tractenberg R, Schneider JA, Crane PK, Bennett DA (2014) A 2-process model for neuropathology of Alzheimer's disease. *Neurobiol Aging* **35**, 301-308.

[54] Foster JK, Albrecht MA, Savage G, Lautenschlager NT, Ellis KA, Maruff P, Szoeke C, Taddei K, Martins R, Masters CL, Ames D (2013) Lack of reliable evidence for a distinctive epsilon4-related cognitive phenotype that is independent from clinical diagnostic status: Findings from the Australian Imaging, Biomarkers and Lifestyle Study. *Brain* **136**, 2201-2216.

[55] Huang Y, Mahley RW (2014) Apolipoprotein E: Structure and function in lipid metabolism, neurobiology, and Alzheimer's diseases. *Neurobiol Dis* **72 Pt A**, 3-12.

[56] Jack CR Jr, Wiste HJ, Weigand SD, Knopman DS, Vemuri P, Mielke MM, Lowe V, Senjem ML, Gunter JL, Machulda

MM, Gregg BE, Pankratz VS, Rocca WA, Petersen RC (2015) Age, sex, and APOE epsilon4 effects on memory, brain structure, and beta-amyloid across the adult life span. *JAMA Neurol* **72**, 511-519.

[57] Jack CR Jr, Knopman DS, Jagust WJ, Petersen RC, Weiner MW, Aisen PS, Shaw LM, Vemuri P, Wiste HJ, Weigand SD, Lesnick TG, Pankratz VS, Donohue MC, Trojanowski JQ (2013) Tracking pathophysiological processes in Alzheimer's disease: An updated hypothetical model of dynamic biomarkers. *Lancet Neurol* **12**, 207-216.

[58] Ashford JW, Atwood CS, Blass JP, Bowen RL, Finch CE, Iqbal K, Joseph JA, Perry G (2005) What is aging? What is its role in Alzheimer's disease? What can we do about it? *J Alzheimers Dis* **7**, 247-253; discussion 255-262.

[59] Ashford JW, Shan M, Butler S, Rajasekar A, Schmitt FA (1995) Temporal quantification of Alzheimer's disease severity: 'Time index' model. *Dementia* **6**, 269-280.

[60] Ashford JW, Schmitt FA (2001) Modeling the time-course of Alzheimer dementia. *Curr Psychiatry Rep* **3**, 20-28.

[61] Ashford JW, Furst AJ (2014) Advancing brain imaging for Alzheimer's disease: Integrating anatomic and physiologic measures. *J Alzheimers Dis* **41**, 759-763.

[62] Darreh-Shori T, Hosseini SM, Nordberg A (2014) Pharmacodynamics of cholinesterase inhibitors suggests add-on therapy with a low-dose carbamylating inhibitor in patients on long-term treatment with rapidly reversible inhibitors. *J Alzheimers Dis* **39**, 423-440.

[63] Lane RM, Darreh-Shori T (2015) Understanding the beneficial and detrimental effects of donepezil and rivastigmine to improve their therapeutic value. *J Alzheimers Dis* **44**, 1039-1062.

[64] Doody RS, Geldmacher DS, Gordon B, Perdomo CA, Pratt RD (2001) Open-label, multicenter, phase 3 extension study of the safety and efficacy of donepezil in patients with Alzheimer disease. *Arch Neurol* **58**, 427-433.

[65] Grossberg G, Irwin P, Satlin A, Mesenbrink P, Spiegel R (2004) Rivastigmine in Alzheimer disease: Efficacy over two years. *Am J Geriatr Psychiatry* **12**, 420-431.

[66] Raskind MA, Peskind ER, Truyen L, Kershaw P, Damaraju CV (2004) The cognitive benefits of galantamine are sustained for at least 36 months: A long-term extension trial. *Arch Neurol* **61**, 252-256.

[67] Raskind MA, Peskind ER, Wessel T, Yuan W (2000) Galantamine in AD: A 6-month randomized, placebo-controlled trial with a 6-month extension. The galantamine USA-1 study group. *Neurology* **54**, 2261-2268.

[68] Wilcock G, Howe I, Coles H, Lilienfeld S, Truyen L, Zhu Y, Bullock R, Kershaw P (2003) A long-term comparison of galantamine and donepezil in the treatment of Alzheimer's disease. *Drugs Aging* **20**, 777-789.

[69] Mintzer JE, Kershaw P (2003) The efficacy of galantamine in the treatment of Alzheimer's disease: Comparison of patients previously treated with acetylcholinesterase inhibitors to patients with no prior exposure. *Int J Geriatr Psychiatry* **18**, 292-297.

[70] Bandyopadhyay S, Goldstein LE, Lahiri DK, Rogers JT (2007) Role of the APP non-amyloidogenic signaling pathway and targeting alpha-secretase as an alternative drug target for treatment of Alzheimer's disease. *Curr Med Chem* **14**, 2848-2864.

[71] Lichtenthaler SF (2012) Alpha-secretase cleavage of the amyloid precursor protein: Proteolysis regulated by signaling pathways and protein trafficking. *Curr Alzheimer Res* **9**, 165-177.

[72] Fisher A (2012) Cholinergic modulation of amyloid precursor protein processing with emphasis on M1 muscarinic receptor: Perspectives and challenges in treatment of Alzheimer's disease. *J Neurochem* **120**(Suppl 1), 22-33.

[73] Ashford JW (2002) ApoE4: Is it the absence of good or the presence of bad? *J Alzheimers Dis* **4**, 141-143.

[74] Chakrabarti A, Chatterjee A, Sengupta MB, Chattopadhyay P, Mukhopadhyay D (2013) Altered levels of amyloid precursor protein intracellular domain-interacting proteins in Alzheimer disease. *Alzheimer Dis Assoc Disord* **28**, 283-290.

[75] Ashford JW, Bayley PJ (2013) Retrogenesis: A model of dementia progression in Alzheimer's disease related to neuroplasticity. *J Alzheimers Dis* **33**, 1191-1193.

[76] Mufson EJ, Mahady L, Waters D, Counts SE, Perez SE, DeKosky ST, Ginsberg SD, Ikonomovic MD, Scheff SW, Binder LI (2015) Hippocampal plasticity during the progression of Alzheimer's disease. *Neuroscience*, doi: 10.1016/j.neuroscience.2015.03.006

[77] Drachman DA, Leavitt J (1974) Human memory and the cholinergic system. A relationship to aging? *Arch Neurol* **30**, 113-121.

[78] Robert PH, Benoit M (2008) Neurochemistry of cognition: Serotonergic and adrenergic mechanisms. *Handb Clin Neurol* **88**, 31-40.

[79] Alkon DL, Sun MK, Nelson TJ (2007) PKC signaling deficits: A mechanistic hypothesis for the origins of Alzheimer's disease. *Trends Pharmacol Sci* **28**, 51-60.

[80] Lucke-Wold BP, Turner RC, Logsdon AF, Simpkins JW, Alkon DL, Smith KE, Chen YW, Tan Z, Huber JD, Rosen CL (2015) Common mechanisms of Alzheimer's disease and ischemic stroke: The role of protein kinase C in the progression of age-related neurodegeneration. *J Alzheimers Dis* **43**, 711-724.

[81] Sun MK, Alkon DL (2014) The "memory kinases": Roles of PKC isoforms in signal processing and memory formation. *Prog Mol Biol Transl Sci* **122**, 31-59.

[82] Zisopoulou S, Asimaki O, Leondaritis G, Vasilaki A, Sakellaridis N, Pitsikas N, Mangoura D (2013) PKC-epsilon activation is required for recognition memory in the rat. *Behav Brain Res* **253**, 280-289.

[83] Ashford JW, Coburn KL, Fuster JM (1998) Functional cognitive networks in primates. In *Fundamentals of Neural Networks: Neuropsychology and Cognitive Neuroscience*, Parks RW, Levine DS, eds. The MIT Press, Cambridge, Mass.

[84] Alkon DL, Rasmussen H (1988) A spatial-temporal model of cell activation. *Science* **239**, 998-1005.

[85] Alkon DL (1989) Memory storage and neural systems. *Sci Am* **261**, 42-50.

[86] Taylor AB, Fallon JR (2006) Dendrites contain a spacing pattern. *J Neurosci* **26**, 1154-1163.

[87] Ashford JW, Coburn KL, Rose TL, Bayley PJ (2011) The topography of P300 energy loss in aging and Alzheimer's disease. *J Alzheimers Dis* **26**(Suppl 3), 229-238.

[88] Masliah E, Cole G, Shimohama S, Hansen L, DeTeresa R, Terry RD, Saitoh T (1990) Differential involvement of protein kinase C isozymes in Alzheimer's disease. *J Neurosci* **10**, 2113-2124.

[89] Flammang B, Pardossi-Piquard R, Sevalle J, Debayle D, Dabert-Gay AS, Thevenet A, Lauritzen I, Checler F (2012) Evidence that the amyloid-beta protein precursor intracellular domain, AICD, derives from beta-secretase-generated C-terminal fragment. *J Alzheimers Dis* **30**, 145-153.

[90] Um JW, Kaufman AC, Kostylev M, Heiss JK, Stagi M, Takahashi H, Kerrisk ME, Vortmeyer A, Wisniewski T, Koleske AJ, Gunther EC, Nygaard HB, Strittmatter SM (2013) Metabotropic glutamate receptor 5 is a coreceptor for Alzheimer abeta oligomer bound to cellular prion protein. *Neuron* **79**, 887-902.

[91] Cao X, Sudhof TC (2004) Dissection of amyloid-beta precursor protein-dependent transcriptional transactivation. *J Biol Chem* **279**, 24601-24611.

[92] Cao X, Sudhof TC (2001) A transcriptionally [correction of transcriptively] active complex of APP with Fe65 and histone acetyltransferase Tip60. *Science* **293**, 115-120.

[93] Saganich MJ, Schroeder BE, Galvan V, Bredesen DE, Koo EH, Heinemann SF (2006) Deficits in synaptic transmission and learning in amyloid precursor protein (APP) transgenic mice require C-terminal cleavage of APP. *J Neurosci* **26**, 13428-13436.

[94] Zhou F, Gong K, Song B, Ma T, van Laar T, Gong Y, Zhang L (2012) The APP intracellular domain (AICD) inhibits Wnt signalling and promotes neurite outgrowth. *Biochim Biophys Acta* **1823**, 1233-1241.

[95] Ashford JW, Soultanian NS, Zhang SX, Geddes JW (1998) Neuropil threads are collinear with MAP2 immunostaining in neuronal dendrites of Alzheimer brain. *J Neuropathol Exp Neurol* **57**, 972-978.

[96] Scheff SW, Price DA (2006) Alzheimer's disease-related alterations in synaptic density: Neocortex and hippocampus. *J Alzheimers Dis* **9**, 101-115.

[97] Masliah E, Terry RD, DeTeresa RM, Hansen LA (1989) Immunohistochemical quantification of the synapse-related protein synaptophysin in Alzheimer disease. *Neurosci Lett* **103**, 234-239.

[98] Brewer GJ, Cotman CW (1989) NMDA receptor regulation of neuronal morphology in cultured hippocampal neurons. *Neurosci Lett* **99**, 268-273.

[99] Lazzeroni LC, Halbauer JD, Ashford JW, Noda A, Hernandez B, Azor V, Hozack N, Hasson N, Henderson VW, Yesavage JA, Tinklenberg JR (2013) Memantine is associated with longer survival than donepezil in a Veterans Affairs prescription database, 1997 to 2008. *J Alzheimers Dis* **36**, 791-798.

[100] Dang V, Medina B, Das D, Moghadam S, Martin KJ, Lin B, Naik P, Patel D, Nosheny R, Ashford JW, Salehi A (2014) Formoterol, a long-acting beta2 adrenergic agonist, improves cognitive function and promotes dendritic complexity in a mouse model of Down syndrome. *Biol Psychiatry* **75**, 179-188.

[101] Greco SJ, Hamzelou A, Johnston JM, Smith MA, Ashford JW, Tezapsidis N (2011) Leptin boosts cellular metabolism by activating AMPK and the sirtuins to reduce tau phosphorylation and beta-amyloid in neurons. *Biochem Biophys Res Commun* **414**, 170-174.

[102] Czirr E, Leuchtenberger S, Dorner-Ciossek C, Schneider A, Jucker M, Koo EH, Pietrzik CU, Baumann K, Weggen S (2007) Insensitivity to Abeta42-lowering nonsteroidal anti-inflammatory drugs and gamma-secretase inhibitors is common among aggressive presenilin-1 mutations. *J Biol Chem* **282**, 24504-24513.

[103] Cote S, Carmichael PH, Verreault R, Lindsay J, Lefebvre J, Laurin D (2012) Nonsteroidal anti-inflammatory drug use and the risk of cognitive impairment and Alzheimer's disease. *Alzheimers Dement* **8**, 219-226.

[104] Kaufman AC, Salazar SV, Haas LT, Yang J, Kostylev MA, Jeng AT, Robinson SA, Gunther EC, van Dyck CH, Nygaard HB, Strittmatter SM (2015) Fyn inhibition rescues established memory and synapse loss in Alzheimer mice. *Ann Neurol* (Epub ahead of print) Feb. 23, 2015, pages 1-19.

[105] Nygaard HB, Wagner AF, Bowen GS, Good SP, MacAvoy MG, Strittmatter KA, Kaufman AC, Rosenberg BJ, Sekine-Konno T, Varma P, Chen K, Koleske AJ, Reiman EM, Strittmatter SM, van Dyck CH (2015) A phase Ib multiple ascending dose study of the safety, tolerability, and central nervous system availability of AZD0530 (saracatinib) in Alzheimer's disease. *Alzheimers Res Ther* **7**, 35.

[106] Bredesen DE (2014) Reversal of cognitive decline: A novel therapeutic program. *Aging (Albany NY)* **6**, 707-717.

[107] Schneider LS, Mangialasche F, Andreasen N, Feldman H, Giacobini E, Jones R, Mantua V, Mecocci P, Pani L, Winblad B, Kivipelto M (2014) Clinical trials and late-stage drug development for Alzheimer's disease: An appraisal from 1984 to 2014. *J Intern Med* **275**, 251-283.