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Commentary

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

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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

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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.

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