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APOE ε4 Allele-associated Alzheimer's disease risk is consistent with increased lifetime exposure to a neurotoxic process

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Abstract

In the adult human brain, approximately one trillion synapses are constructed and deconstructed daily as part of normal learning and memory. A growing body of evidence suggests that Alzheimer's disease (AD) is characterized by dysregulated neuroplasticity processes that initially shift the balance toward synaptic loss causing poor episodic memory, while later changes induce synaptic slaughter causing dementia. Inheritance of a single copy of the apolipoprotein E (APOE) ε4 allele has been shown to increase the risk of AD by 3-4-fold, with homozygosity associated with a 12-16-fold increase in risk. Further, there is a decrease of risk associated with the APOE ε2 allele. The pathological consequence of APOE genotype, accounting for the vast majority of AD risk, has led to intense efforts to understand the mechanistic basis of the interplay between APOE status and loss of synapses. Studies conducted across the age spectrum from infancy through senescence have demonstrated that APOE ε4-positive status is associated with increased brain activity and macromolecule turnover in young healthy individuals, with the reverse extant in elderly subjects. The recent demonstration that the brains of APOE ε4-positive healthy young adults utilize approximately 16% more of the lipid membrane constituent docosahexaenoic acid (DHA) opens the possibility that part of the increased long-term neurotoxicity might be explained by pharmacokinetics. For example, if the hippocampal neurons of two individuals possess the same susceptibility to either an endogenous or exogenous stress factor, the neurons with the highest turnover of proteins, lipids, and other macromolecules would experience a larger integrated dose of detriment. Small differences in pharmacokinetic effects might be amplified by the extremely long prodromal phase of AD, *i.e.,* average age of presentation for a homozygous ε4 is about 68 years of age.

Introduction

A central concept in toxicology is the dose-response relationship [1], with toxicity usually increasing with total dose. Dose-response curves can take different shapes including linear, sigmoidal, survival (Gompertz curve), natural logarithmic, parabolic, and even an inverted u-shape in the case of hormesis [2]. Host factors [3] and co-exposures can play an important role in susceptibility to a variety of factors [4]. Many tissues exhibit a redundancy which when exceeded heralds the onset of clinical symptoms [5].

Parkinson's disease (PD) reportedly follows the pattern of a disease process whose symptoms are manifested when the number of surviving neurons decreases below a certain level. The earliest symptoms of motor dysfunction have been consistently estimated to present at around 30% loss of the dopaminergic neurons in the *substantia nigra* of the basal ganglia [6]. Similarly, the early symptoms of memory loss associated with Alzheimer's disease (AD) also present after a large number of neurons have already been lost [7]. In contrast with the 30% neuronal loss of dopamine neurons calculated to be associated with the appearance of PD symptoms, the more diffuse pathology of AD, affecting several types of neurons, cortical regions, and neuronal systems, renders quantitative estimation of AD loss more difficult, though the factor most closely related pathologically to dementia is synapse loss [8,9].

While the neuropathology of Alzheimer's disease, first described by Alzheimer in 1906 [10] is characterized by the presence of neuritic plaques (composed of β-amyloid deposits and neurites made of hyperphosphorylated microtubule associated protein-tau, pTAU) [11] and intracellular neurofibrillary tangles (composed of pTAU) [12], these pathological features are no longer considered as causative of dementia or AD itself. Rather, these pathological hallmarks of AD are now viewed more appropriately as representing the incidental results or scars of complex processes which lead initially to impaired neuroplastic processes subserving memory and later to synaptic slaughter causing dementia [13,14].

In principle, AD is a disease of neuroplasticity [15-18]. Several different molecules and molecular processes which are central to neuroplasticity are likely candidates for contributing to the episodic memory impairment characteristic of early AD and the dementia of later AD phases, including projections from the brain stem [19,20] by the norepinephrine neurons of the locus coeruleus [21] and serotonergic neurons of the midbrain raphe nuclei [22]. Despite the diversity of candidates there is general agreement that loss of synapses is the closest correlate of the memory impairment and dementia of AD across the continuum of cognitive dysfunction [23,24].

It is notable that the brain regions most susceptible to AD-associated synaptic loss are regions with normally high rates of synapse turnover,

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both formation and removal, and a high number of synaptic connections per neuron, particularly the hippocampus [25]. The importance of synaptic remodeling, including by exuberant synaptogenesis and synaptolysis during critical periods of brain development [26], for normal adult brain function [27], and in pathological processes [28] has stimulated intense study. This effort has revealed that hundreds of different proteins displaying a series of signaling and structural functions play a role in synapse formation and normal removal [29]. In addition to the complex array of protein interactions, the formation of and remodeling-associated loss of synapses also involves significant turnover of a number of lipid components of the pre- and post-synaptic membrane [30].

Importance of the APOE Genotype

The APOE genotype accounts for the vast majority of AD risk and AD pathology [31,32]. There are three common alleles of the APOE gene, *i.e.,* APOE ε2, APOE ε3, and APOE ε4 [33]. In the general US population, the ε4 allele prevalence is approximately 13% [34]. In contrast with unaffected individuals in the US, over 50% of patients with non-familial AD carry the ε4 allele [18]. Possession of one ε4 allele increases the risk of developing AD by 3 to 4-fold, and possession of two ε4 alleles increases risk by 15-fold, as compared with the ε3/ ε3 genotype [35].

This profound difference in AD risk results from only minor changes in the structure of the APOE molecule. The three isoforms of APOE differ in amino acid sequence at only chain positions 112 and 158: the APOE ε2 allele has cysteine at both positions; the APOE ε4 allele has arginine at both positions; and the APOE ε3 allele has cysteine at position 112 and arginine at 158 [36]. These small changes in amino acid sequence alter the biological activity of the APOE proteins in multiple ways, one of which is increased liver catabolism of the APOE ε4 lipoprotein as compared with the APOE ε3 lipoprotein [37,38].

Recently, Yassine*, et al.* [39] used positron emission tomography to demonstrate increased docosahexaenoic acid (DHA) uptake in several brain regions in APOE ε4 carriers. In the AD-susceptible entorhinal sub-region, the mean global gray matter DHA incorporation coefficient was 16% higher among APOE ε4 carriers (n = 9) than among APOE ε3 and APOE ε2 carriers (n = 13, p = 0.046). These results might be especially significant given that DHA is concentrated at synapses, and comprises up to 40% of the fatty acids in gray matter [40].

Paradoxical increase in brain activity and cognitive performance in young healthy APOE ε4-positive subjects

The dominant role played by the APOE ε4 allele in development of AD [35], has elicited intense interest in the mechanism of APOE ε4 control of factors related to AD, particularly the amyloid protein precursor, APP [41], how APOE may be involved in neuroplasticity [42], and the role of APOE in controlling molecules related to AD and neuroplasticity [43]. A number of studies have demonstrated that although the APOE ε4 allele is associated with reduced cognition in many elderly subjects [18] just the opposite has been shown in young subjects possessing the APOE ε4 allele. APOE ε4-positive infants display enhanced mental development [44]. In a Finnish study on 1577 children, motor activity and mental vitality increased significantly by APOE genotype in the ascending order of ε2/2, ε3/2, ε4/2, ε3/3, ε4/3, and ε4/4 [45]. A study conducted on 147 school-aged children reported that ε4-positive children performed better on a visuospatial task than did ε2-positive children [46]. Higher performance on an IQ test was shown for ε4-positive young females in China [47]. Increased verbal fluency across six decades of age span has been reported for ε4-positive subjects [48]. As compared with ε3/ε3 subjects, during a working memory task an ε3/ε4 group displayed greater brain activation in the medial prefrontal and parietal regions bilaterally, and in the right dorsolateral prefrontal cortex during a working memory task [49] While increased brain activation during a task may be an indication that neural systems are less efficient for information processing [50], such an increase could also represent a larger number of cortical resources and involved synapses available for processing incoming information. In a study in 340 young healthy volunteers, a Swiss group measured better episodic memory in ε4 subjects as compared with either ε3 or ε2 carriers [51]. In summary, a comprehensive but not exhaustive review of the literature demonstrates that the APOE ε4 allele is associated with increased brain activity and mental performance in healthy, young individuals.

Synaptic toxicity increases with macromolecular turnover rate

The increased rate of DHA incorporation into neuronal membranes reported by Yassine *et al.* [39], and higher brain activity seen in young, healthy APOE ε4-positive individuals both support a higher rate of turnover in synaptic macromolecules associated with the APOE ε4 allele, regardless of explanation. Although neurogenesis can occur in the adult hippocampus [52], and increased neurogenesis increases the rate of synapse formation, synaptogenesis and synaptic pruning occur in the absence of neurogenesis. Synapses are extremely small and incredibly dynamic. It has been estimated that the human brain contains 100 billion neurons, of which 10 billion are pyramidal neurons found in the cerebral cortex. Each of these pyramidal neurons can fire approximately 1,000 times per second. There are approximately 10^{15} synapses in the brain, *i.e.,* a quadrillion, with the average half-life of a synapse being about 100 days [53]. Synapse turn-over rates in the brain vary widely anywhere from 15 minutes in the hippocampus [54] to many years in the stable primary cortical regions. Rarely appreciated is the necessity of the adult human brain to prune daily approximately the same number of synapses that it forms as a normal part of learning and memory. The number of synapses formed and actively removed is estimated to be one trillion per day. Given the need to remove so many synapses, it is not surprising that the brain would possess a robust system for synaptic remodeling, *i.e.,* an intrinsic homeostatic capacity for synapse creation and non-pathological synaptotoxicity [55-57].

Although oxidative stress might contribute to the disruption of neuroplasticity seen in AD, the purpose of the following discussion is to illustrate the general principle that toxic insults can accumulate sequentially from repeated exposures. Current technology is not able to measure small errors that occur in lipid and protein composition, and three-dimensional architectural defects propagated during the construction and deconstruction of synapses. In contrast, at the larger cellular level where measurements are possible, non-repaired errors in DNA replication are common. The nervous system is vulnerable to DNA damage for a variety of reasons. First, neurons experience relatively high exposure to reactive oxygen species based on their high mitochondrial respiration rates [58]. Second, the limited capacity for adult neurons to proliferate can lead to the accumulation of mutational damage [59]. Third, neurons stay in G_0, *i.e.,* the quiescent or resting phase of the cell cycle and therefore employ the relatively error prone method of DNA repair termed non-homologous end joining [60]. Fourth, oxidative DNA damage can block transcription, and neurons are heavily dependent on transcription [61]. Fifth, vulnerable neurons display an exuberant inflammatory response [62]. The larger number of biochemical reactions occurring per unit time in the brains of

APOE ε4 individuals as compared with APOE ε3 individuals would increase the total lifetime exposure to potentially harmful oxidative species. Similarly, given that increased brain activity and biochemical reaction rate are seen in APOE ε4 positive infants and children, lifetime exposure to either internally generated neurotoxic macromolecules, or exogenous environmental pathogens or toxins would be increased. The remaining question in Alzheimer's disease is exactly how APOE genotype, presumably through mechanisms related to the production or metabolism of APP, leads to disruption of synapse formation, impaired memory, an excess of synaptic pruning and retraction, with induction of hyperphosphorylation of TAU, leading to massive synapse loss and dementia.

The Gompertz law of survival and AD

The Gompertz survival function represents a fundamental model of the aging process [63-65], and depends on the initial mortality rate and the doubling time of that rate. The Gompertz curve is applicable across the evolutionary spectrum. In the year 2000, the Gompertz survival function accounted for 99.7% of the variance in mortality rates for those over the age of 30 in the United States. Across that age span, mortality doubled every 8.2 years for men and 7.5 years for women [18].

The Alzheimer's literature is replete with the statement that AD is not part of normal aging [66]. The incidence of AD doubles approximately every five years in the population over 60. However, Ashford [18] has compared the Gompertz survival function doubling time of 7.5 and 8.2 years with the five-year doubling time for AD incidence and shown that AD tracks age more closely than mortality. The normalcy versus pathogenicity of AD can be viewed from evolutionary and demographic perspectives. In 1900, the average lifespan in the United States was 47.8 years (both sexes combined) [67]. AD was not a common cause of death in 1900. In contrast, given the current expansion of lifespans, approximately one-third of all men and two-thirds of all women in the US will contract AD prior to death. Only a limited number of other medical conditions approach the ubiquity of distribution displayed by AD in the elderly population, e.g., cataracts in whites over 80 (70%) [68]. As a point of comparison, acute macular degeneration with neovascular degeneration occurs in only 15% of white women over age 80 living in the United Kingdom [69].

Until 300,000 years ago, ancestors of modern humans were ubiquitously ε4/ε4 and then the ε3 allele mutated from the ancestral ε4 allele [70]. The ε3 allele displayed a competitive survival advantage sufficiently robust to result in the current predominance of the ε3/ε3 genotype which is now found in over 60% of the US population [18]. Similarly, the ε2 allele mutated from the ε3 allele about 200,000 years ago, but this protective allele has remained relatively rare with the homozygous ε2/ε2 variant less than 1%, and the ε3/ε2 heterozygote in about 11% of the population [71].

Conclusion

If the hippocampal neurons of two individuals possess the same susceptibility to either an endogenous or exogenous stress factor, the neurons with the highest turnover of proteins, lipids, and other macromolecules would experience a larger integrated dose of detriment. Small differences in pharmacokinetic effects might be amplified by the extremely long prodromal phase of AD, *i.e.,* average age of presentation for a homozygous ε4 is about 68 years of age.

Given the ancestral primacy of the ε4 allele, and the evolutionary trade-off of superior performance in youth versus additional years beyond historical lifespans, the abnormality of the ε4 allele is somewhat a matter of perspective. If part of the APOE ε4-associated neurotoxic susceptibility is based on pharmacokinetic rather than toxicant-receptor interactions on a per mole basis, future therapies that slow down synaptic pruning might carefully consider differential effects based on APOE allele subtype. Current knowledge of potential sources of Alzeimer's patient heterogeneity is lacking. Reducing at least one important source of inter-subject heterogeneity, *i.e.,* apolipoprotein allele frequency, is advisable. Early attempts at shifting the balance away from synaptic pruning might consider enrolling early stage Alzheimer's patients possessing at least one ε4 allele.

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