Decreased Clearance of CNS β-Amyloid in Alzheimer's Disease

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Alzheimer's disease (AD) is characterized by increased amounts of soluble and insoluble β-amyloid (Aβ), predominantly in the form of Aβ42 in amyloid plaques and Aβ40 in amyloid angiopathy. The amyloid hypothesis proposes that AD is caused by an imbalance between Aβ production and clearance (*1*), resulting in increased amounts of Aβ in various forms such as monomers, oligomers, insoluble fibrils, and plaques in the central nervous system (CNS). High levels of Aβ then initiate a cascade of events culminating in neuronal damage and death manifesting as progressive clinical dementia of the Alzheimer's type (*2*).

In rare cases of AD, genetic alterations increase the production of Aβ (*3*). However, Aβ dysregulation in the far more common late-onset "sporadic" AD is less well understood. Possible mechanisms of increased Aβ production for late-onset AD include alterations in gamma or beta secretase activity. Alternatively, impaired clearance of Aβ may also cause late-onset AD through interactions with ApoE4, decreased catabolism of Aβ via reduced proteolysis, impaired transport across the blood-brain barrier, or impaired cerebrospinal fluid (CSF) transport.

To measure the production and clearance of Aβ in AD, we developed a method to measure human CNS Aβ production and clearance (fig. S1) (*4*) and compared Aβ42 and Aβ40 production and clearance rates in individuals with symptomatic AD and in cognitively normal persons to determine whether either or both are altered in AD.

We plotted the average time course results of labeled Aβ42 and Aβ40 for the production phase (hours 5 to 14) and the clearance phase (hours 24 to 36) (Fig. 1). The production and clearance rates were calculated for each participant and compared by group status (AD versus control). The average Aβ42 production rate did not differ between the control (6.7%/hour) and AD (6.6%/hour) groups ($P = 0.96$), nor did Aβ40 production rate differ between groups (6.8%/hour for controls and 6.8%/hour for the AD group; $P = 0.98$). The average clearance rate of Aβ42 was slower for AD individuals compared with that for cognitively normal controls (5.3%/hour versus 7.6%/hour, $P = 0.03$), as was the average clearance rate of Aβ40 (5.2%/hour for AD individuals versus 7.0%/hour for controls; $P = 0.01$).

To determine the balance of Aβ production to clearance rates in AD versus controls, we measured the ratios of production to clearance (fig. S2). The ratio of Aβ42 production to clearance rates was balanced for cognitively normal participants (0.95); however, because of decreased clearance in the AD participants, there was an imbalance in the Aβ42 production to clearance ratio (1.35). Similarly, we observed an imbalance in the AD Aβ40 production to clearance ratio (1.37) compared with the ratio in cognitively normal participants (0.99).

The technique of measuring Aβ production and clearance has been used to measure effects of drugs that target Aβ generation, demonstrating decreases in production (*5*). We found that late-onset AD is associated with a 30% impairment in the clearance of both Aβ42 and Aβ40, indicating that Aβ clearance mechanisms may be critically important in the development of AD (*6*). Estimates based on a 30% decrease in Aβ clearance rates suggest that brain Aβ accumulates over about 10 years in AD. The impaired clearance of both Aβ40 and Aβ42 is consistent with prior findings of deposition of Aβ40 and Aβ42 in parenchymal amyloid plaques and the substantial deposition of Aβ40 in cerebral amyloid angiopathy in about 80% of cases of AD (*7*).

Limitations of this study include the relatively small numbers of participants (12 in each group) and the inability to prove causality of impaired Aβ clearance for AD. In addition to decreased CNS Aβ clearance, CSF Aβ42 concentrations are decreased in AD compared with those in controls (fig. S3). Taken together, these may be consistent with decreased Aβ42 clearance (efflux) from the brain to the CSF. However, the relationship between decreased concentrations of CSF Aβ42 and decreased CNS clearance of labeled Aβ (fig. S4) is not fully understood. Additional possibilities include more than one pool of Aβ in CSF, undetected pools of Aβ in CSF by enzyme-linked immunosorbent assay (e.g., oligomers), or a combined increase in Aβ production with impaired efflux from parenchyma to CSF. Overall, these results suggest impaired metabolism of Aβ in AD compared with that in controls.

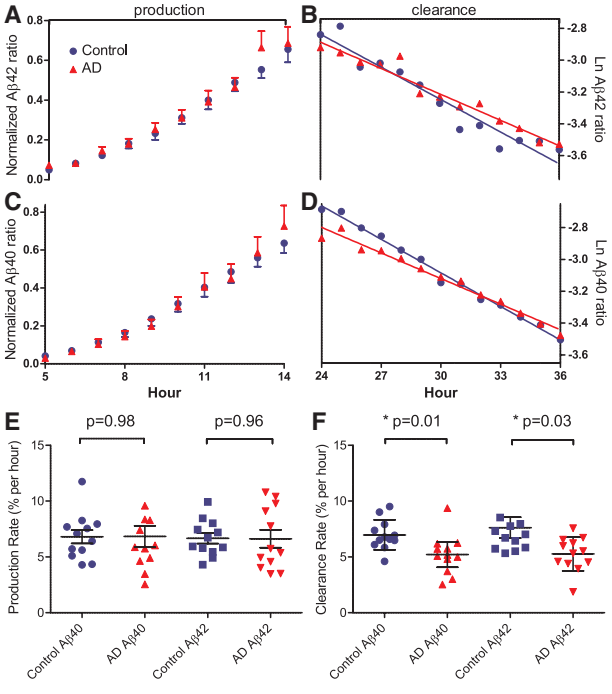

Fig. 1. Aβ kinetics in the CNS of 12 AD participants (red triangles) and 12 controls (blue circles). The amount of labeled Aβ42 and Aβ40 was measured and compared between groups to measure production and clearance rates of both Aβ species. Error bars indicate SEM. (**A**) Normalized labeled Aβ42 production phase. (**B**) Aβ42 clearance phase. (**C**) Normalized labeled Aβ40 production phase. (**D**) Aβ40 clearance phase. (**E**) Fractional synthesis rates of Aβ42 and Aβ40. (**F**) Fractional clearance rates of Aβ42 and Aβ40.

References and Notes

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Supporting Online Material

www.sciencemag.org/cgi/content/full/science.1197623/DC1
Materials and Methods
Figs. S1 to S4
References

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