

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 (A β), predominantly in the form of A β 42 in amyloid plaques and A β 40 in amyloid angiopathy. The amyloid hypothesis proposes that AD is caused by an imbalance between A β production and clearance (1), resulting in increased amounts of A β in various forms such as monomers, oligomers, insoluble fibrils, and plaques in the central nervous system (CNS). High levels of A β 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 A β (3). However, A β dysregulation in the far more common late-onset "sporadic" AD is less well understood. Possible mechanisms of increased A β production for late-onset AD include alterations in gamma or beta secretase activity. Alternatively, impaired clearance of A β may also cause late-onset AD through interactions with ApoE4, decreased catabolism of A β via reduced proteolysis, impaired transport across the blood-brain barrier, or impaired cerebrospinal fluid (CSF) transport.

To measure the production and clearance of A β in AD, we developed a method to measure human CNS A β production and clearance (fig. S1) (4) and compared A β 42 and A β 40 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 A β 42 and A β 40 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 A β 42 production rate did not differ between the control (6.7%/hour) and AD (6.6%/hour) groups ($P = 0.96$), nor did A β 40 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 A β 42 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 A β 40 (5.2%/hour for AD individuals versus 7.0%/hour for controls; $P = 0.01$).

To determine the balance of A β production to clearance rates in AD versus controls, we measured the ratios of production to clearance (fig. S2). The ratio of A β 42 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 A β 42 production to clearance ratio (1.35). Similarly, we observed an imbalance in the AD A β 40 production to clearance ratio (1.37) compared with the ratio in cognitively normal participants (0.99).

The technique of measuring A β production and clearance has been used to measure effects of drugs that target A β generation, demonstrating decreases in production (5). We found that late-onset AD is associated with a 30% impairment in the clearance of both A β 42 and A β 40, indicating that A β clear-

ance mechanisms may be critically important in the development of AD (6). Estimates based on a 30% decrease in A β clearance rates suggest that brain A β accumulates over about 10 years in AD. The impaired clearance of both A β 40 and A β 42 is consistent with prior findings of deposition of A β 40 and A β 42 in parenchymal amyloid plaques and the substantial deposition of A β 40 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 A β clearance for AD. In addition to decreased CNS A β clearance, CSF A β 42 concentrations are decreased in AD compared with those in controls (fig. S3). Taken together, these may be consistent with decreased A β 42 clearance (efflux) from the brain to the CSF. However, the relationship between decreased concentrations of CSF A β 42 and decreased CNS clearance of labeled A β (fig. S4) is not fully understood. Additional possibilities include more than one pool of A β in CSF, undetected pools of A β in CSF by enzyme-linked immunosorbent assay (e.g., oligomers), or a combined increase in A β production with impaired efflux from parenchyma to CSF. Overall, these results suggest impaired metabolism of A β in AD compared with that in controls.

References and Notes

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Materials and Methods
Figs. S1 to S4
References

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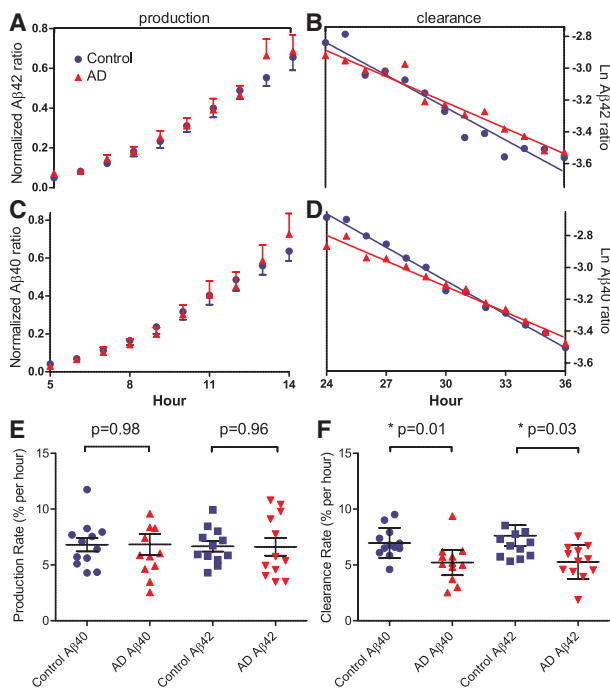


Fig. 1. A β kinetics in the CNS of 12 AD participants (red triangles) and 12 controls (blue circles). The amount of labeled A β 42 and A β 40 was measured and compared between groups to measure production and clearance rates of both A β species. Error bars indicate SEM. (A) Normalized labeled A β 42 production phase. (B) A β 42 clearance phase. (C) Normalized labeled A β 40 production phase. (D) A β 40 clearance phase. (E) Fractional synthesis rates of A β 42 and A β 40. (F) Fractional clearance rates of A β 42 and A β 40.

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