Alzheimer's trials: A cul-de-sac with no end in sight

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Abstract

We don't understand Alzheimer, its origin and disease mechanisms. The absence of disease-modifying treatments for Alzheimer today is due to the amyloid hypothesis, a misguided hypothesis of Alzheimer's disease etiology, which has dominated Alzheimer research, drug development, and clinical trials for 30 years. However, the hypothesis is not dead yet, as exemplified by the recent resurrection of clinical trials with aducanumab. Recent advances in Alzheimer research include astrocytes, synaptic function and glutamate signaling. Many studies indicate EAAT2 as a promising target in drug discovery and clinical development for novel therapies in Alzheimer's disease, and other neurologic and psychiatric diseases.

Key words: Alzheimer's disease, clinical trials, drug discovery, EAAT2

Introduction

Understanding and treatment of disease go hand in hand. A case in point, the topic of this Editorial, is Alzheimer's disease (AD), the most devastating disorder of the human mind and the major cause of dementia. Despite decades of research efforts in academia and the drug industry, and hundreds of clinical trials, we have no cure, no prevention and no treatment for AD. Why is that? The short answer is that we do not understand AD – its origin and disease mechanisms.

Trials and failures

The long answer is as follows. In the early 1900s, when Alois Alzheimer and many others described amyloid plaques and neurofibrillary tangles in the post-mortem brains of senile people, they did not propose any cause or effect. Do the plaques and tangles cause dementia, or does dementia cause the plaques and tangles? Indeed, in 1911 Alzheimer wrote: "There is then no tenable reason to consider these cases as caused by a specific disease process."[1] The amyloid hypothesis proposes Aβ peptide accumulation and amyloid formation in the brain cause AD. The hypothesis has almost singularly guided AD research and clinical trials ever since it was formulated 30 years ago.[2] Yet, several facts and experimental studies are against the hypothesis.[3–8] All AD trials, hundreds of them over the years, whether with β- or γ-secretase inhibitors to reduce Aβ peptides production or with anti-Aβ antibodies to clear amyloid from the brain, have failed to stop or slow the cognitive decline or improve the daily living of AD patients. Similarly, in preventive trials in cognitively unimpaired people at high

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risk of developing AD, due to the *APOE4* gene or elevated PET scan-determined brain amyloid, reducing Aβ peptide production and amyloid did not prevent or slow cognitive decline. The most definitive evidence against the hypothesis, however, comes from the recent preventive trials in cognitively unimpaired people carrying the presenilin *PS1* mutation E280A, which causes AD at the age of 49. Trials with the anti-Aβ antibodies solanezumab or ganterumab failed to prevent or slow the cognitive decline. Even worse, the preventive trials and treatment methods intended to help often harmed many study participants volunteering for the trials by causing serious health problems, including enhanced cognitive decline.

Challenges in research

If these AD trials and failures do not prove the amyloid hypothesis wrong, then what does? And if these trials and errors do not ring the bell and call for a major change in AD research, and question the rationales of AD research policy making, then what does?

It is fair to say the absence of disease-modifying treatments for AD today is due to the amyloid hypothesis, a misguided hypothesis of AD etiology, which has dominated research, drug development and clinical trials for 30 years. In 2014, when Jack de la Torre was writing in *The New England Journal of Medicine*: "[...] when is a dead hypothesis really dead?", he was commenting on the failed trials in AD patients with the anti-Aβ antibodies solanezumab and bapineuzumab.[9] However, the hypothesis is not dead yet, as exemplified by the recent resurrection of clinical trials with aducanumab.[10] On June 7, 2021, the US Food and Drug Administration (FDA) approved the use of aducanumab (Aduhelm™) to treat AD.[11]

In 1991, Swash et al. wrote: "Recent advances in Alzheimer's disease imply a need for adequate clinical trials of new treatments which require careful design."[12] Today, recent advances in AD research have investigated astrocytes, synaptic function and glutamate signaling. In neurotransmission, synaptic glutamate signaling is regulated by the glutamate transporter EAAT2 expressed on astrocytes (which cover the synapses). As soon as glutamate signaling starts, it is stopped within 1 ms by EAAT2, which binds and removes glutamate from the synapses. This prevents excessive glutamate signaling, which can lead to synapse loss and neuron cell death, the early signs of developing AD. In mouse models of AD, increasing EAAT2 expression slows disease progression, whereas decreasing EAAT2 expression enhances disease progression. Human postmortem AD brains have less EAAT2. These observations, and many other studies, indicate EAAT2 as a promising target in drug discovery and clinical development of novel therapies in AD and other neurologic and psychiatric diseases.[13–15]

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