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REVIEW ARTICLE

Review of the advances in treatment for Alzheimer disease: strategies for combating β-amyloid protein☆

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Abstract
Introduction: Alzheimer disease (AD) is a major neurodegenerative disorder which eventually results in total intellectual disability. The high global prevalence and the socioeconomic burden associated with the disease pose major challenges for public health in the 21st century. In this review we focus on both existing treatments and the therapies being developed, which principally target the β-amyloid protein.
Discussion: The amyloidogenic hypothesis proposes that β-amyloid plays a key role in AD. Several pharmacological approaches aim to reduce the formation of β-amyloid peptides by inhibiting the β-secretase and γ-secretase enzymes. In addition, both passive and active immunotherapies have been developed for the purpose of inhibiting β-amyloid peptide aggregation.
Conclusions: Progress in identifying the molecular basis of AD may provide better models for understanding the causes of this neurodegenerative disease. The lack of efficacy of solanezumab (a humanised monoclonal antibody that promotes β-amyloid clearance in the brain), demonstrated by 2 recent Phase III clinical trials in patients with mild AD, suggests that the amyloidogenic hypothesis needs to be revised.

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Una revisión de los avances en la terapéutica de la enfermedad de Alzheimer: estrategia frente a la proteína β-amiloide

Resumen
Introducción: La enfermedad de Alzheimer (EA) es el principal trastorno neurodegenerativo que provoca una discapacidad intelectual total en los pacientes que la presentan. La elevada prevalencia a nivel mundial, así como la elevada carga socioeconómica que conlleva la EA para la sociedad en general, hace que sea considerada un importante problema de salud pública en este siglo XXI. En este trabajo se revisan los tratamientos actuales y en fase de desarrollo que actúan principalmente sobre la proteína β-amiloide.
Discusión: La hipótesis amiloidogénica propone que el péptido β-amiloide tiene un papel clave en esta enfermedad. Se han desarrollado varias estrategias farmacológicas diferentes con el objetivo de inhibir la formación de los péptidos β-amiloides, como son los inhibidores de β-secretasa y γ-secretasa. Además, se han desarrollado los tratamientos antiamiloide, que incluyen inmunoterapias pasivas y activas enfocadas a inhibir la agregación del péptido β-amiloide.
Conclusiones: Los avances en la identificación de las bases moleculares de la EA pueden servir como modelo para comprender las causas de esta enfermedad neurodegenerativa. Sin embargo, los ensayos clínicos más recientes en 2 ensayos de fase III con solanezumab, un anticuerpo monoclonal humanizado que promueve el aclaramiento del β-amiloide en el cerebro, indican que este anticuerpo no muestra eficacia en pacientes con EA leve, sugiriendo que hay que replantearse esta hipótesis amiloidogénica de la EA.

Introduction

Alzheimer disease (AD) is a neurodegenerative disease with a progressive course and the most frequent cause of dementia in the worldwide population older than 65 (50-70% of all dementia cases).[1] This chronic and progressive disease gives rise to deficits in multiple brain functions (mainly at the cortical and hippocampal levels); these include memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgement.[2] Alterations contributing to cognitive deficit are accompanied by deterioration in emotional control and social behaviour.

Considering the disease's high prevalence and heavy socioeconomic costs for society at large, AD is regarded as an important public health problem. In fact, statistics indicate that it may constitute the 'pandemic of the 21st century', making it a priority for medical research today. Despite the major scientific and clinical advances made in AD research in the last 30 years, the treatments that are currently available are all symptomatic, that is, they lessen the symptoms of the disease by acting on different levels of the neuropathological process.[2] Although they can improve patients' quality of life, none of them is truly able to slow the rapid, fatal progression of the disease.

At present, only 4 currently available drugs have been approved for treating AD. They belong to 2 groups: the acetylcholinesterase inhibitors (AChEI) and the N-methyl-D-aspartate receptors (NMDAR). Donepezil, rivastigmine, and galantamine belong to the AChEI group.[2–4] The action mechanism of AChEI drugs is to increase cholinergic transmission by means of inhibiting acetylcholinesterase in the synaptic cleft; this process could increase the cognitive capacity of AD patients somewhat. Memantine is an NMDAR antagonist; it reduces excitotoxicity by blocking that ionotropic receptor, since levels of the excitatory neurotransmitter glutamate are pathologically high in AD. Both drug groups are indicated as treatment for patients in moderate stages of AD.[3,4] Nevertheless, it has been shown that none of these approved drugs has a real curative effect; they are only a palliative measure, and their effectiveness decreases over time.

Researchers continue to explore new treatments and therapeutic strategies in order to slow the course of the disease. Above all, these measures are designed for multiple targets and intended for use in the early stages of AD, given the neuropathological complexity of the disease.

If these future treatments are to be effective, doctors must develop new diagnostic techniques that will enable AD diagnosis in its preclinical phase (before symptoms appear) or even able to predict AD before it develops.

AD prevention poses a feasible challenge, but for this goal to be achieved, we must gain a better understanding of the aetiology of AD and how environmental and lifestyle factors affect risk of developing the disease.

Aetiology: proposed hypotheses, risk factors, and protective factors

The cause or causes of AD are unknown, although different hypotheses have been proposed to explain the complex neurodegenerative process underlying this disease.[5–8] Most experts agree that it develops as a result of the