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Review

Alzheimer's disease: New therapeutic strategies☆

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ABSTRACT

The rapid increase in prevalence rates of Alzheimer's disease means that treatments to prevent, stop or reverse this devastating disease are urgently needed. Despite advances in understanding its molecular pathology, there are no drugs that can halt its progression. This review takes a tour through phase 2, or higher studies, probing receptor agonist agents interfering with aggregation, inhibitors/modulators of secretases, lipid-lowering agents, and, finally and most extensively, immunotherapy. The fact that phase 3 studies with bapineuzumab and solaneuzumab have recently failed does not invalidate the potential of immunotherapy, as more information is available and new clinical trials are being initiated.

Enfermedad de Alzheimer: nuevas estrategias terapéuticas

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RESUMEN

El rápido aumento de las tasas de prevalencia de la enfermedad de Alzheimer hace que se necesiten con urgencia tratamientos dirigidos a prevenir, detener o revertir esta devastadora enfermedad. A pesar de los avances en la comprensión de su patología molecular, todavía no existen fármacos que puedan detener su progresión. Esta revisión hace un recorrido por aquellos estudios en fase 2, o superior, que ensayan agonistas de receptores, sustancias que interfieren en la agregación, inhibidores/moduladores de las secretasas, hipolipidemiantes, y, finalmente y con mayor extensión, las inmunoterapias. El hecho de que recientemente hayan fallado las fases 3 para bapineuzumab y solaneuzumab no invalida el potencial de la inmunoterapia, ya que cada vez disponemos de más información y se están iniciando nuevos ensayos clínicos.

Introduction

In their 2013 report, the Alzheimer's Disease International Organisation, estimated that there were 44.4 million people with dementia worldwide at that time and most cases were attributable to AD.[1] Future projections on the prevalence of the disease are startling, with an estimated 75.6 million cases by the year 2030 and 134.5 million by 2050; therefore, AD is considered a 21st century pandemic. Because the neurodegenerative process can extend over more than a decade, the associated dementia causes suffering to both the patient and their carers, with the consequent social impact. Accordingly, the global economic impact is enormous, the estimated expenditure being 600,000 million dollars for 2010 alone.[2]

In Spain, the prevalence of dementia in 2013 was around 600,000 cases, 67% with AD and 33% with other types of dementia, particularly dementia of vascular origen.[3] Bearing in mind that Spain is one of the European countries with the most ageing population, the future projections are extremely worrying.

At present, there are two types of drugs which have been approved by agencies such as the Food and Drug Administration (U.S.A.) or the European Medicines Agency for treating the symptoms of AD. The first acts on the cholinergic system and the second on the glutamatergic system. Because the disease's main outcome is the death of cholinergic neurones, increased acetylcholine levels partially compensate for the loss of this neurotransmitter.[4] Cholinesterase, donepezil, galantamine and rivastigmine inhibitors

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are used for this purpose. Furthermore, it is known that glutamate increases in patients with AD, as in other neurodegenerative diseases, and that this imbalance results in cell death. Memantine, an N-methyl-D-aspartate receptor antagonist, a subtype of glutamate ionotropic receptors is used for its neuroprotective effect.[5] However, these treatments do not halt the progression of the disease, they have a beneficial effect only in some stages, and are very variable depending on the patient.

Aetiopathology of Alzheimer's disease

The principal histological features of AD are a considerable reduction in the number of cortical cells, and the presence of two types of protein structures, extracellular amyloid plaques and intracellular neurofibrillary tangles. The main component of amyloid deposits is a 4 kDa peptide, named the Aβ peptide, which is generated by limited proteolysis of the amyloid precursor protein (APP protein), a transmembrane protein.[6] Neurofibrillary tangles are composed of aberrant microtubule-associated tau, generally hyperphosphorylated and fragmented. Unlike that which occurs with the Aβ peptide, abnormal tau metabolism is linked to other neurodegenerative diseases, known collectively as tauopathies.[7]

Depending on the age at which it starts, AD is classified as early-onset, EOAD or late-onset, LOAD, the age between early and late onset being approximately 65. Although 1% to 2% of cases of AD are classified as early onset, fewer than half correspond to the familiar form, which is inherited as an autosomal trait of high penetrance. Non-familial early onset AD is classified along with late onset AD in that it is known as the sporadic form of the disease.

Three genes which cause familial AD are known: the amyloid precursor protein gene (*APP*, chromosome 21), the presenilin 1 gene (*PSEN1*, chromosome 14) and the presenilin 2 gene (*PSEN2*, chromosome 1). The fact that the APP gene is located in chromosome 21 results in a gene dosis effect in Down's syndrome, causing early onset. The presenilins are the constituent enzymes of the secretase complexes which are in charge of processing APP. Missense mutations of the *PSEN1* gene are the most common cause of familial AD.[8]

The amyloid cascade hypothesis was proposed, based on this information, in which the accumulation of the Aβ peptide in the form of amyloid plaques will trigger the disease. In the last decade it has been demonstrated that the so-called Aβ oligomers are the precursors of these plaques, the cause of the toxicity that leads to neuronal death.[9]

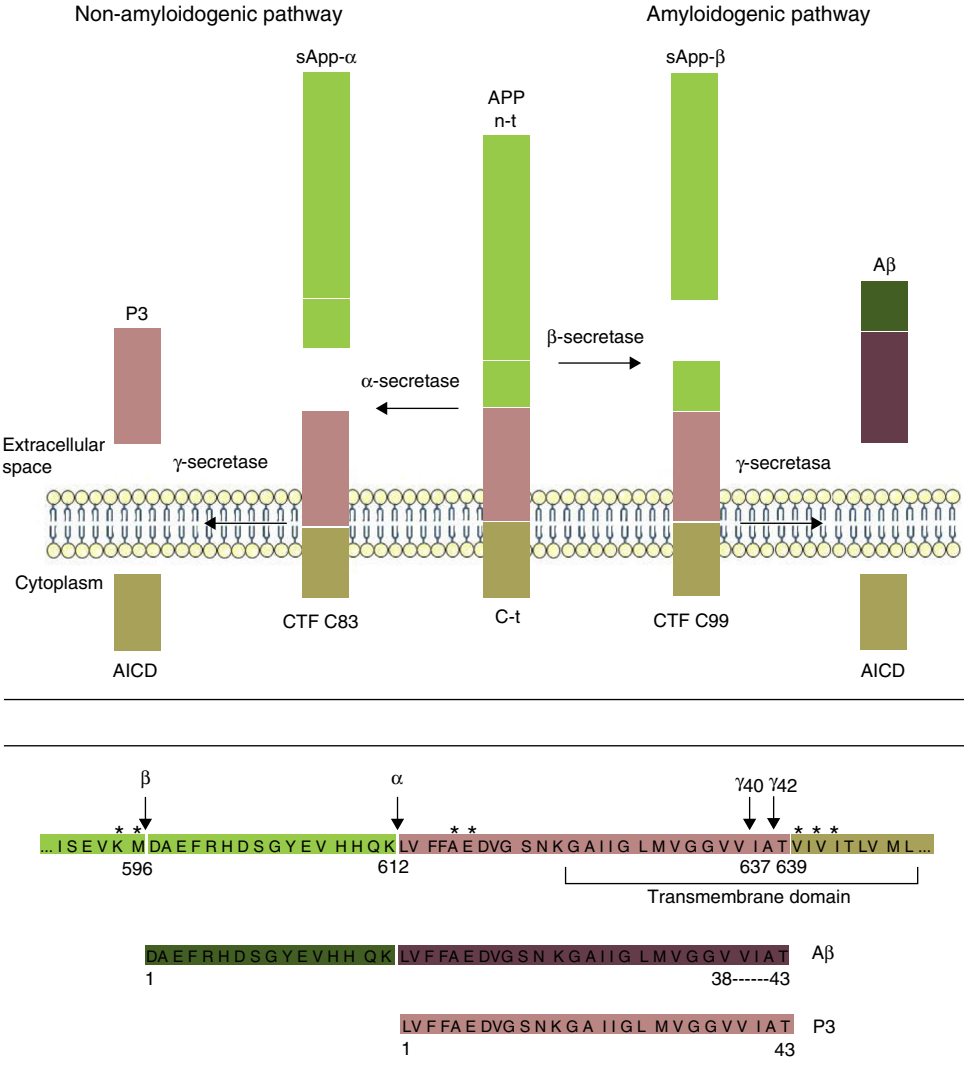

Fig. 1. APP can follow 2 proteolytic processing pathways: the non- amyloidogenic pathway and the amyloidogenic pathway. (A) Upper panel, the action of γ-secretase on fragments C83 and C99 generates the P3 peptide and Aβ peptide, respectively. (B) Lower panel, the Aβ peptide changes in size from 38 to 43 residues; forms 40 and 42 are predominant. Form 42 is the most amyloidogenic because the 2 extra residues that the C-terminal end contains are hydrophobic.