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Review Article

New Therapeutic Targets in Alzheimer's Disease☆

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SUMMARY

Up to the present, the identification of neurochemical alterations underlying Alzheimer's disease allowed for the development of the first generation of therapies that are somewhat specific for this disorder. Although both cholinesterase inhibitors and NMDA receptor blockade have well-proven efficacy levels, the clinical outcomes of patients receiving such treatments are rather limited; with many authors considering them as "symptomatic" treatments. In this context, it is safe to say that although the microscopic alterations present in AD have been well known for over a century, we have failed to identify therapeutic agents able to block the synthesis and aggregation of amyloid β42 or the formation of neurofibrillary tangles. Some new therapeutic strategies have however been explored in the last few years. This paper aimed at reviewing the evidence supporting these new "disease modifying" therapeutic options, including anti-amyloid and anti-Tau strategies.

1. Introduction

In-depth understanding of the pathogenic mechanisms involved in the determinism of Alzheimer's disease (AD) and also that of other dementias could open new horizons for the development of new disease-modifying therapeutic strategies.

The current view is that there are two main processes that are both characteristic and determinant in the pathogenesis of AD: the formation and deposition of amyloid plaques and the formation of neurofibrillary tangles[1] (Figure 1). The formation of amyloid plaques is explained by the "amyloid cascade hypothesis". It states that the pathogenic process starts either because of mutations in the amyloid precursor protein (APP), or due to other mutations and environmental factors. These changes lead to the formation of amyloidogenic peptides that first aggregate into oligomers, which can interfere with synaptic neurotransmission (e.g. cholinergic neurotransmission), and then into amyloid plaques, which are thought to cause intracellular metabolic alterations that lead to the hyperphosphorylation of tau proteins[2]. Hyperphosphorylated tau proteins then aggregate to form neurofibrillary tangles that alter intracellular metabolism to a sufficient degree to cause neuronal death. Both amyloid plaques and neurofibrillary tangles are thought to cause an excessive release of glutamate in certain cortical and sub-cortical structures[3] that can lead to neuronal death through N-methyl-D-aspartate (NMDA) receptor mediated excitotoxicity[4].

Up to the present, the identification of neurochemical alterations allowed for the development of the first generation of therapies that are somewhat specific for AD. Studies have shown that cholinergic neurons are the first to be lost, more so in AD[5]. Furthermore, acetylcholine transferase (ChaT) markers are absent, and choline up-take and acetylcholine release are reduced in AD[6]. As a result, the first therapeutic approach was aimed at correcting the reduction of cholinergic neurotransmission through cholinesterase inhibitors (e.g. rivastigmine, donepezil, galantamine). On the other hand, extensive research has shown that AD is characterized by alterations in cortical and subcortical glutamatergic structures[3,4]. Therefore, another therapeutic approach is based on NMDA receptor blockade (e.g. memantine).

Although both cholinesterase inhibitors and NMDA receptor blockade have well-proven efficacy levels, the clinical outcomes of patients receiving such treatments are rather limited, many authors considering them as "symptomatic" treatment[7–11].

In this context, it is safe to say that although the microscopic alterations present in AD have been well known for over a century, we have failed to identify therapeutic agents able to block the synthesis and aggregation of amyloid β42 (Aβ42) or the formation of neurofibrillary tangles. Some new therapeutic strategies have however been explored in the last few years.

☆ Conflicts of interest: All contributing authors declare that they have no conflicts of interest.

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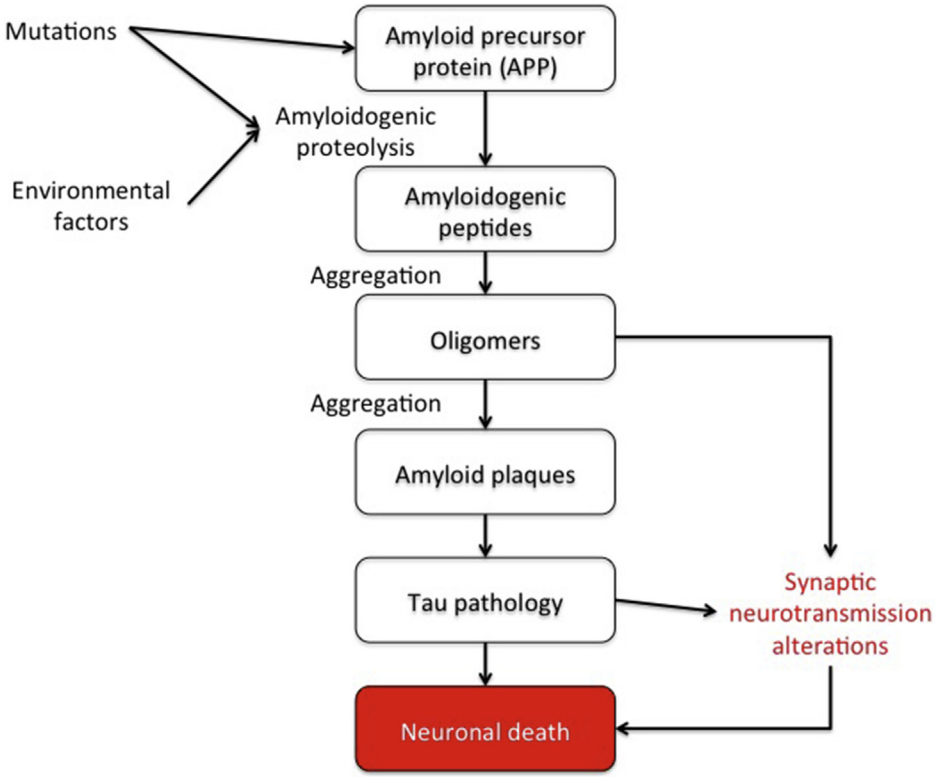

Figure 1. Neurobiological mechanisms involved in the pathogenesis of Alzheimer's disease.

This paper aimed at reviewing the evidence supporting these new "disease modifying" therapeutic options, including anti-amyloid and anti-Tau strategies. We searched the PubMed database using the Medical Subject Heading (MeSH) term "Alzheimer Disease/Therapy" for full-text articles written in English that were published between January 1990 and January 2016. The articles were then selected for inclusion based on their relevance to the aim of this review.

2. Anti-amyloid strategies

APP has two distinct metabolic pathways, in which the action of three secretases is key (Figure 2). First, the non-amyloid metabolization involves the proteolysis of APP under the action of α-secretase, which produces a soluble fragment known as α-APP and a smaller 83 amino-acids long peptide. This smaller peptide is then further cleaved by γ-secretase into two non-amyloidogenic peptides[2]. Amyloid synthesis is impossible in this case because α-secretase cleaves APP in the middle of the fragment that forms the amyloidogenic peptides[12]. Second, the amyloid metabolization involves the proteolysis of APP under the action of β-secretase. This results in the production of another soluble fragment called β-APP and a 91 amino-acid long peptide that is further cleaved by γ-secretase, releasing amyloidogenic peptides (Aβ40, Aβ42 and Aβ43)[13].

New anti-amyloid agents target the inhibition or stimulation of secretases involved in the metabolism of APP, the selective reduction of the synthesis of Aβ42, the prevention of amyloid aggregation and anti-amyloid immunotherapy[14].

2.1. Secretase inhibition or stimulation

A number of γ-secretase inhibitors are currently under research. Semagacestat (LY450139) is a non-selective γ-secretase inhibitor under testing in numerous clinical trials. Two of these phase III clinical trials that included patients with mild to moderate AD were prematurely interrupted. Both of them were initiated in March 2008 and were interrupted by the sponsor (Eli Lilly) in August 2008 due to significant worsening in cognitive function[15]. Furthermore, γ-secretase inhibitors were found to be associated with hepatic, splenic and cutaneous adverse events[16].

β-secretase inhibition could also limit the synthesis of Aβ42[17], and several such products are currently tested in clinical trials, i.e. CTS-21166 (CoMentis), PF-05297909 (Pfizer), LY2886721 (Lilly), AZD3293 (AstraZeneca) or MK-8931 (Merk)[18]. The phase I clinical trial for CTS-21166 reported a dose dependent reduction in plasma Aβ levels[15]. Further encouraging results have been obtained in preclinical studies of AZD3293 and the product is now under investigation in a combined phase II/III clinical trial to test its disease-modifying properties[19].

α-secretase can be stimulated by stimulating protein kinase C (PKC), and this has been proven to reduce the formation of Aβ42 in laboratory animals. PKC in turn can be stimulated through multiple neurotransmission pathways. For instance, muscarinic receptor 1 (M1) agonists have been proven to increase non-amyloidogenic proteolysis of APP and to decrease the production of Aβ42[17].

2.2. Selective reduction of Aβ42 synthesis

Agents in this class are generically known as SALA (selective Aβ42-lowering agents).

Tarenflurbil is the first representative of this class. Its mechanism of action is the allosteric modulation of the activity of γ-secretase aimed to modify the proteolysis of APP so that the synthesis of Aβ42 is replaced by the synthesis of Aβ38, a polypeptide with significantly lower neurotoxic effects[20,21]. A phase II clinical trial which included 207 patients diagnosed with mild AD concluded that patients with mild cognitive impairment that were given 1600 mg tarenflurbil BID had a significantly slower