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Review article

Nanotechnology-based drug delivery systems for Alzheimer's disease management: Technical, industrial, and clinical challenges

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ABSTRACT

Alzheimer's disease (AD) is a neurodegenerative disease with high prevalence in the rapidly growing elderly population in the developing world. The currently FDA approved drugs for the management of symptomatology of AD are marketed mainly as conventional oral medications. Due to their gastrointestinal side effects and lack of brain targeting, these drugs and dosage regiments hinder patient compliance and lead to treatment discontinuation. Nanotechnology-based drug delivery systems (NTDDS) administered by different routes can be considered as promising tools to improve patient compliance and achieve better therapeutic outcomes. Despite extensive research, literature screening revealed that clinical activities involving NTDDS application in research for AD are lagging compared to NTDDS for other diseases such as cancers. The industrial perspectives, processability, and cost/benefit ratio of using NTDDS for AD treatment are usually overlooked. Moreover, active and passive immunization against AD are by far the mostly studied alternative AD therapies because conventional oral drug therapy is not yielding satisfactorily results. NTDDS of approved drugs appear promising to transform this research from 'paper to clinic' and raise hope for AD sufferers and their caretakers. This review summarizes the recent studies conducted on NTDDS for AD treatment, with a primary focus on the industrial perspectives and processability. Additionally, it highlights the ongoing clinical trials for AD management.

Contents

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1. Introduction

Alzheimer's disease (AD) is the most common type of dementia within the elderly population [1]. It is a progressive neurodegenerative disease which can be diagnosed in elderly patients affected with memory loss. Other symptoms include thinking disorders, impaired communication, changes in behavior, ill orientation, or difficulties in coordination and eating. Up-to-date, AD represents the leading cause of death in Europe and the sixth cause of death in the US and it affects the normal life of the patients and their families with huge economic consequences. In the US, it is estimated that annual societal and economic cost of dementia is $818 billion, and it is expected to become a trillion dollar in just three years' time [2]. This very high cost is due to the expensive treatments in addition to financial burdens for caregivers or hospital care in advanced cases.

AD diagnosis is rapidly progressing due to the increasing prevalence. AD patients manifest symptoms in three stages consisting of mild, moderate and severe dementia. Sperling and coworkers recommended in 2011 a new classification [3] where preclinical AD stage and mild cognitive impairment (MCI) stage were included before the aforementioned three dementia stages. In the MCI stage, people are diagnosed with brain changes, such as atrophy, indicating onset of AD symptoms within 15–20 years. During MCI, people suffer from mild thinking disorders that does not affect their ability to perform their daily activities (i.e. without needing help). In the later dementia stages, some patients show classical AD symptoms and then start requiring assistance.

2. Alzheimer's disease: neuropathogenesis, therapeutic targets and treatments

AD progression is gradual and slow, and may begin 20 or more years before clinical symptoms are apparent [4,5]. AD might run in some families and is defined as 'familial AD', which accounts for nearly 5–10% of all AD cases [6]. The primary genes implicated in familial AD are those for presenilins 1 and 2, alpha-2 macroglobulins, and Apo-E. On the other hand, sporadic (non-familial) AD, accounting for about 70% of AD cases, and are due to a combination of genetic, environmental, and lifestyle factors [6].

Several hypotheses were proposed to explain AD pathogenesis on a molecular level. Understanding all the key players in AD neuropathogenesis will help identify possible therapeutic targets. AD could therefore be managed using symptomatic or targeted disease-modifying treatments. Symptomatic treatment strategies improve cognition and memory; hence recover a better quality of life [7]. The proposed theories of AD pathogenesis include three different approaches based on cholinergic, amyloid, and tau hypotheses. Besides these major hypothesis, there is evidence that reactive oxygen species (ROS), nitric oxide, and inflammatory mediators might also contribute to the pathogenesis of AD [8].

2.1. Amyloid cascade hypothesis

Amyloid precursor protein (APP) is a type 1 transmembrane glycoprotein that is expressed in several cell types. The proteolysis of APP is regulated by α-, β- and γ-secretases (Fig. 1 A). The amyloid cascade hypothesis proposes that altered APP proteolysis drives the accumulation of amyloid proteins [$A\beta_{(1\rightarrow 40)}$ and $A\beta_{(1\rightarrow 42)}$]; which progressively aggregate into oligomers, fibrils and plaques. These accumulated protein aggregates are toxic, inducing neurodegeneration, cytotoxicity, and inevitably leading to dementia manifestations (Fig. 1A) [9,10]. In 1984, Glenner and Wong successfully identified and purified amyloid protein in the cerebrospinal fluid of AD patients [11]. Based on this hypothesis, several anti-amyloid therapies have been proposed and studied including rosiglitazone, pioglitazone, and semagacestat [12].

2.2. Cholinergic hypothesis

It is the earliest hypothesis explaining AD pathogenesis. Discovery of reduced choline uptake and acetylcholine release of AD patients brain samples indicated substantial presynaptic cholinergic deficit, thus leading to memory impairment and cognition defectiveness [8]. Cholinergic drugs are usually cholinesterase inhibitors (ChEIs) that enhance the cholinergic neurotransmission by inhibiting acetylcholine esterase (Fig. 1B). The FDA-approved ChEIs include donepezil, rivastigmine, and galantamine [13].

2.3. Excitotoxicity hypothesis

N-methyl-D-aspartate (NMDA) receptor is essential for controlling synaptic plasticity and memory function [14]. It is activated when glutamate and glycine bind to it, allowing Ca^{2+} and Na^{+} influx (Fig. 1C). It has been reported that the hyperexcitability of NMDA receptors induces Ca^{2+} overload, triggering a cascade of events, and leading eventually to apoptosis [14]. Glutametergic drugs, such as the FDA-approved memantine, are uncompetitive NMDA receptor antagonists for the symptomatic treatment of moderate to severe AD [14] (Fig. 1C).

2.4. Tau hypothesis

A normal mature neuron has three microtubule-associated protein (MAP) taus; MAP1A, MAP1B, and MAP2. They are responsible for promoting the assembly and stability of microtubules [15]. The biological activity of tau is regulated by its degree of phosphorylation [16]. In AD brains, tau is abnormally hyperphosphorylated, which impairs its binding to microtubules; leading to the accumulation of neurofibrillary tangles and dementia [16]. Several anti-tau therapies have been studied including lithium, valproate, and nicotinamide [12] (Fig. 1D).

2.5. Mitochondrial cascade hypothesis

Substantial growing evidence suggests that a defective energy metabolism in the mitochondria might contribute to the pathogenesis of AD [17]. Genetic mutations altering the regulation of the electron transport chain complex enzymes are capable of generating ROS; leading to cell apoptosis and neurodegeneration [17]. Several drugs targeting the mitochondrial dysfunction have been investigated such as latrepirdine [18].