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Alzheimer's disease therapies: Selected advances and future perspectives

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Abstract Among the neurodegenerative diseases, Alzheimer's disease (AD) represents one of the biggest challenges that the modern health care system has to deal with. The lack of data about the etiology and the complexity of the underlying pathogenesis constitute the biggest struggle facing the development of new therapeutical approaches. Within this paper we describe selected currently used approaches, point some challenges and give indications about the future perspectives in AD treatments. We hope this paper together with the selected references will contribute in putting spot light on the future of AD therapies and give guidelines for both professionals and researches working on that area of the brain diseases.

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1. Introduction

One of the major challenges facing the modern health care system is the neurodegenerative diseases such as Alzheimer's disease (AD)[1] that represents the most prevalent dementia.[1] AD represents a neurodegenerative disorder characterized by loss of neurons, cognition[2] and a progressive loss of brain

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functions.[3] This disorder affects a large number of the human population, for instance in USA alone more than 5 million people suffer from AD.[4] AD has heavy medical, economic and social consequences due not only to AD itself but also due to the related problems such as dementia, both dependency and disability among older people[5] and vascular impairment.[6]

Although the AD-related neurodegenerative process remains unclear,[7] description of some pathogenic processes has been reported. AD is associated with the aggregation of abnormal proteins[2] including amyloid beta (Aβ)protein[5,8] that aggregate into senile plaques[9] in the brains of AD patients[8] and the pathologically modified tau[9] which are hyperphosphorylated[5] and that aggregate into neurofibrillary tangles[9] in the brain. Both neurons' death and amyloid protein fibril accumulation lead to AD[10] and the accumulation of Aβ in the brain leads to a chain of pathogenic processes n brains of AD patients.[11]

Furthermore, other phenomena have been reported as parts of the AD pathological process including altered synaptic function,[12] Cerebral amyloid angiopathy[13] and functional and morphological impairment of cerebral circulation.[6] Importantly, neuroinflammation is also a key element within AD pathogenesis.[14] Theses diverse elements reflect the different targets we can consider for AD therapeutic approaches.

2. Selected therapeutic advances

At present, current drug treatments of AD, such as cholinesterase inhibitors or NMDA antagonists,[1] mainly help to manage symptoms[5] hereby obviating the need for new approaches to deal with AD underlying mechanisms. Indeed, some current therapeutic approaches include reversible cholinesterase inhibitor like rivastigmine.[2]

Epidemiological studies have important contributions to presenting new bases for future. For instance, risks of developing Alzheimer's disease can be decreased by smoking tobacco and it was suggested that nicotine inhibits neuronal apoptosis which prevents the Aβ25–35-induced neurotoxicity[15] pointing a starting point to new therapeutic approaches.

Natural products described by pharmacognosy constitute important resources for AD treatment especially after modern sciences have built bridges between Traditional Chinese Medicines and modern pharmacology.[16] For instance, Malay traditional practitioners claimed that Aquilaria subintegra leaves can treat AD patients, supposedly via Acetyl choline inhibition[17] and the amyloid formation could be inhibited by Silymarin which is a standardized extract of milk thistle.[18] In addition, since inflammation is an element within AD pathogenesis[14], extracts or compounds from plants with anti-Inflammatory properties such as *Nigella glandulifera* Freyn et Sint[19] could provide a complementary therapy.

Importantly, different findings and ways for research deserve more attention. Molecules that inhibit Amyloid-β such as pinocembrin,[11] emerging therapeutic targets for the treatment of AD including Glucagon-like peptide-1[14] represent good examples. Moreover, both the development of animal models of AD[20] and the description of molecules implicated in diverse pathogenesis such as cyclic peptides[10] and the Aβ-targeted immunotherapy[5] and cysteinyl leukotriene receptor 1 antagonism[21] sphingosine 1-phosphate receptor[22] 5-HT4 receptor-induced α-secretase activation[23] bring more hope toward identifying new targets.

3. Perspectives and challenges

The new methods including ultrasound[6] and positron emission tomography[24] help for the early AD diagnosis. Furthermore, they allow us to follow the disease evolution during treatment and potentially identify new therapeutic targets. Indeed, AD development may be related to metabolic disorders like type-2 diabetes mellitus, insulin resistance, metabolic syndrome and obesity.[25] Moreover, Epidemiological data[15,25] diverse traditional medicines,[17] animal studies[25] and the recent investigations about AD cellular and molecular aspects[5] also provide strong starting points to develop new therapeutic approaches for AD.

Diverse approaches are under investigation and some have already shown promising results in AD patients. The immunotherapies that increase Aβ accumulation in preclinical models[5] and metabolic-based therapies[25] represent good examples. We should extend our fields of thinking beyond antiamyloid therapy for AD.[26] Indeed, Tau-related immunotherapy is expected to see further development toward clinical trials[5] as emerging therapeutic strategies for both tauopathies and AD.[1] Another example for AD treatment is the metal chelation; as metal binding with Aβ has been described.[8] Further approaches to prevent spine degeneration in AD[12] seem urgent. At the same time research about AD must take into consideration the parameters that could influence the AD risks, pathogenesis[5] or prognosis including Patient's gender.[4]

However, AD researches still need to overcome different struggles including the regulations and the legal aspects[27] and the fact that different therapeutic theories require in vivo and biodistribution studies[2] before we see a speed up in the progress of AD researches.

Conflict of interest

None.

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