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News and reviews

Amyloid cascade hypothesis: Pathogenesis and therapeutic strategies in Alzheimer's disease

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ABSTRACT

Alzheimer's disease is an irreversible, progressive neurodegenerative disorder. Various therapeutic approaches are being used to improve the cholinergic neurotransmission, but their role in AD pathogenesis is still unknown. Although, an increase in tau protein concentration in CSF has been described in AD, but several issues remains unclear. Extensive and accurate analysis of CSF could be helpful to define presence of tau proteins in physiological conditions, or released during the progression of neurodegenerative disease. The amyloid cascade hypothesis postulates that the neurodegeneration in AD caused by abnormal accumulation of amyloid beta (Aβ) plaques in various areas of the brain. The amyloid hypothesis has continued to gain support over the last two decades, particularly from genetic studies. Therefore, current research progress in several areas of therapies shall provide an effective treatment to cure this devastating disease. This review critically evaluates general biochemical and physiological functions of Aβ directed therapeutics and their relevance.

Contents

1. Introduction . . . 1
2. Hypothesis of AD pathogenesis . . . 2
2.1. Cholinergic hypothesis . . . 2
2.2. Tau hypothesis . . . 3
2.3. Amyloid cascade hypothesis . . . 3
2.3.1. Genetic studies provide evidence for amyloid cascade hypothesis . . . 4
2.3.2. Role of neuropeptides in amyloid cascade hypothesis . . . 7
2.3.3. Amyloid based therapeutic approaches . . . 8
2.3.4. Other therapeutic approaches . . . 12
3. Conclusion . . . 12
Conflict of interest . . . 12
Acknowledgment . . . 12
References . . . 12

1. Introduction

Alzheimer's disease (AD) was first described in 1907 by German physician, Alois Alzheimer (Stelzma et al., 1995). It is a most common form of dementia which emerged as a major public health issue throughout the world. An estimated 5.2 million American people aged over 65 suffered from Alzheimer's disease and total cost for care was reported to be $200 billion in 2012 (Alzheimer's Association, 2012). In India for the year 2010, 3.7 million Indian people aged over 60 had been identified with dementia and estimated cost for taking care was about $3.417 billion (Alzheimer's and Related Disorders Society of India, 2010). AD is an irreversible, progressive neurodegenerative disorder (Khachaturian and Radebaugh, 1996). It is characterized by a group of symptoms such as cognitive dysfunction and non-cognitive

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dysfunctions. The cognitive dysfunction includes memory loss, language difficulties and executive dysfunction and non-cognitive dysfunctions such as psychiatric symptoms and behavioral disturbances, depression, hallucinations, delusion and agitation (Burns et al., 1990). The cognitive deficits had been detected long before the typical symptoms of AD known as prodromal phase of AD (Dubois, 2000; Petersen et al., 1999). In prodromal AD stage, the neuropathological changes are observed in mesial temporal regions (hippocampal formations, parahippocampal gyrus, and entorhinal cortex) and areas critical for long-term episodic memory (Dubois and Albert, 2004). Therefore, prevention of AD progress could be possible in prodromal AD state but neuroimaging, biomarkers and neuropsychological assessment tests for the diagnosis are not fully specified or generally agreed upon (Caldwell et al., 2014). The symptoms of AD progress from mild to moderate which lead to increase in disease severity, including disordered cognitive function and non-cognitive function (Bali et al., 2010). The cognitive performance declines to such an extent that patients need constant support for daily activities in the final stage of the disease (Burns and lliffe, 2009; Bali et al., 2010). AD is a complex neurodegenerative disorder probably caused by copathogenic interactions between various factors such as genetic, epigenetic and environmental factors (Huang and Mucke, 2012).

Advances in human genetic research have identified two distinct forms of AD such as familial Alzheimer's Disease (FAD) and sporadic Alzheimer's disease (SAD) (Ling et al., 2003; Bertram et al., 2010). The total percentage of FAD has been found nearly about 4–8% or less than the overall AD cases. In humans, FAD is caused due to autosomal dominant mutations in *APP* (Goate et al., 1991), *PSEN1* and *PSEN2* genes (Campion et al., 1995; Cruts et al., 1995; Sherrington et al., 1996). These genes are represented as a major genetic risk factor for AD and are inherited in Mendelian fashion. The sporadic AD is the most common form accounting for 90% of all AD cases (Goedert and Spillantini, 2006). It has also been suggested that the synergistic action of genetic and environmental factors could be responsible for the FAD and SAD forms (Huang and Mucke, 2012). AD can be classified into two forms according to the age of onset into early (<60 years) and late (>60 years) onset (Blennow et al., 2006; Bertram et al., 2010).

The clinical and neuropathological analysis shows that FAD is associated with spastic paraparesis and variant neuropathology including large non-neuritic cotton wool plaques (Crook et al., 1998). Recently, molecular analysis and pedigrees have reported that *PSEN*-1 exon 9 deletion in some family member shows spastic paraparesis and cotton wool plaques (Brooks et al., 2003; Menedez, 2004). In clinical studies differences such as presence of myoclonus and generalized seizures, unusual behavior and psychiatric disorders have been found in between FAD and SAD. On the other hand, neuropathologically numerous cortical cotton wool plaques, neurofibrillary tangles, amyloid angiopathy as well as severe degeneration of the lateral corticospinal tracts have been observed in FAD (Lleo et al., 2006; Crook et al., 1998; Hellstrom-Lindahl et al., 2009). Therefore, differences in amyloid beta (Aβ) level and their regional distribution in FAD and SAD is useful to understand molecular mechanism by which Aβ peptide deposited in these forms may be helpful to develop future therapies.

2. Hypothesis of AD pathogenesis

Despite these complexities, extensive research has laid the foundation of our current understanding of the etiology and pathogenesis of AD (Tanzi, 1999; Tanzi and Bertram, 2001). During the past decades many hypotheses have been put forward for AD pathogenesis (Hardy and Higgins, 1992) as described below.

2.1. Cholinergic hypothesis

It is an oldest hypothesis based on cholinergic dysfunction (Contestabile, 2011). The systematic biochemical investigation of brain from AD patient shows reduction in activity of choline acetyltransferase and acetylcholinesterase in cerebral cortex and all other areas below the normal levels as compared with normal brain (Davies and Maloney, 1976). Bowen and co-workers in 1976 reported the reduction of choline acetyltransferase activity in cerebral cortex of postmortem human brain tissues (Bowen et al., 1976). Also, activities of brain decarboxylase and concentration of neuronin S6 has been affected in agonal state which has resulted in to the cerebral hypoxia (Bowen et al., 1976). *In vitro* study shows that the amyloid beta peptide inhibits cholinergic neurotransmission (Kar et al., 1998; Auld et al., 1998). Other studies demonstrated that, reduction in the number of nicotinic and muscarinic acetyl choline receptor located in presynaptic cholinergic terminals decline cognitive function (Whitehouse et al., 1988; Nordberg et al., 1992).

Currently available drug therapies are based on cholinergic hypothesis (Lleo et al., 2006; Reitz et al., 2011). The biochemical investigation of biopsy tissue (Francis et al., 1993) and post-mortem brain tissues from AD patients showed reduced choline acetyltransferase activity (Wilcock et al., 1982), acetylcholine synthesis (Sims et al., 1983), choline uptake (Rylett et al., 1983) and acetylcholine release (Nilsson et al., 1986). These remarkable observations constituted that degeneration of cholinergic neurons and associated loss of cholinergic neurotransmission in the cerebral cortex and other areas contributed significantly to impairment of cognitive functions in Alzheimer's disease (Bartus et al., 1982). To improve cholinergic neurotransmission, different therapeutic approaches used to develop potentially useful drugs for symptomatic treatment in Alzheimer's disease (Lleo et al., 2006; Contestabile, 2011; Reitz et al., 2011).

Over the last two decades, the development of different strategies including cholinesterase inhibitors, choline precursor, postsynaptic and presynaptic cholinergic stimulation with muscarinic and nicotinic agonist has been investigated (Hebert et al., 2003). However, clinical studies showed that the use of precursor for the presynaptic releasing agent and muscarinic agonists are not effective because of lack of efficacy and unacceptable side effects (Doody et al., 2001; Giacobini, 2000, 2001, 2002). But other studies have depicted beneficial effects of cholinesterase inhibitors on cognitive, functional and behavioral symptoms in AD (Rogers et al., 1998; Corey-Bloom et al., 1998; Tariot et al., 2000; Cummings, 2000). Four cholinesterase inhibitors have been approved by FDA for treatment of mild to moderate AD such as tacrine, donepezil, rivastigmine and galantamine. Tacrine was first widely used inhibitor but later on abandoned due to short half-life, hepatotoxicity and cholinergic side effects (Hong-Qi et al., 2012). Now, second generation inhibitors include donepezil, rivastigmine and galantamine have fewer side effects, longer half-lives, and greater efficacy (Giacobini, 2000, 2002). It has been reported that donepezil is a piperidine derivative which can non-competitively and reversibly inhibits acetylcholinesterase (Seltzer, 2007). Galantamine is a tertiary alkaloid agent and allosterically binds to nicotinic receptors to improve cholinergic function (Scott and Goa, 2000). Rivastigmine is a carbamate derivative that inhibits acetylcholinesterase and butyrylcholinesterase (Onor et al., 2007). Unfortunately, clinical trials based on long-term administration of cholinesterase inhibitors to patients with Mild Cognitive Impairment resulted in failure to reduce the risk or delay the onset of Alzheimer's disease (Raschetti et al., 2007; Contestabile, 2011). Moreover, the adverse effects like gastrointestinal, cardiovascular, neuromuscular risks associated with these inhibitors are not negligible (Francis et al., 1999; Raschetti et al., 2007).

In line with cholinergic hypothesis, another hypothesis put forward based on loss of cholinergic function due to lack of specific neurotrophic hormone. Neurotrophins play key role in regulating neuronal function (Schindowski et al., 2008). The neurotrophin family includes nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), neurotrophin-4 = 5 (NT-4 = 5) and neurotrophin-6 (NT-6) (Lang et al., 2004). NGF plays an important role in development and maintenance of sensory and sympathetic nervous system, cholinergic function of central nervous system, cognition