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Review

Therapeutics of Alzheimer's disease: Past, present and future

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ABSTRACT

Alzheimer's disease (AD) is the most common cause of dementia worldwide. The etiology is multifactorial, and pathophysiology of the disease is complex. Data indicate an exponential rise in the number of cases of AD, emphasizing the need for developing an effective treatment. AD also imposes tremendous emotional and financial burden to the patient's family and community. The disease has been studied over a century, but acetylcholinesterase inhibitors and memantine are the only drugs currently approved for its management. These drugs provide symptomatic improvement alone but do less to modify the disease process. The extensive insight into the molecular and cellular pathomechanism in AD over the past few decades has provided us significant progress in the understanding of the disease. A number of novel strategies that seek to modify the disease process have been developed. The major developments in this direction are the amyloid and tau based therapeutics, which could hold the key to treatment of AD in the near future. Several putative drugs have been thoroughly investigated in preclinical studies, but many of them have failed to produce results in the clinical scenario; therefore it is only prudent that lessons be learnt from the past mistakes. The current rationales and targets evaluated for therapeutic benefit in AD are reviewed in this article.

This article is part of the Special Issue entitled 'The Synaptic Basis of Neurodegenerative Disorders'.

1. Introduction

Alzheimer's disease (AD) is the most common cause of dementia, and with a new case occurring every seven seconds globally, the disease itself is becoming a slow pandemic (Ferri et al., 2005). One person for every 85 individuals can be expected to suffer from AD by the year 2050 (Brookmeyer et al., 2007). AD also imposes tremendous emotional and financial burden to the patient's family and community through the provision of care and loss of wages. The disease maybe classified based on the age of onset into early-onset AD and late-onset AD. Early onset AD accounts for approximately 1%–6% of all cases and manifests roughly between 30 and 60 years. Late onset form accounting for around 90% of cases has an age at onset later than 60 years. Etiology of AD is multifactorial with genetic, environmental, behavioral and developmental components playing a role. The greatest risk factor is advancing age; others being a positive family history, head trauma, female gender, previous depression, diabetes mellitus, hyperlipidemia and vascular factors (Kivipelto et al., 2001). The understanding of the pathophysiology of AD is constantly changing; for instance the tangles, a well known pathological hallmark of AD, earlier thought to be responsible for the disease now rather seem to reflect the damage which the neurons have endured over a long time. The notion that amyloid beta peptide (Aβ) and phosphorylated tau are pathologic molecules is slowly changing, and it seems that they represent a cellular adaptive strategy to oxidative stress. Apart from them, various deranged mechanisms such as chronic oxidative stress, mitochondrial dysfunction, Aβ production, neurofibrillary tangles accumulation, hormone imbalance, inflammation, mitotic dysfunction, calcium mishandling, and genetic components play a role in the disease process. Although the mechanisms are diverse, neuronal death, the inevitable event occurs resulting in AD.

2. Therapeutics in AD

Although AD is known for about a century (Ramirez-Bermudez, 2012), four cholinesterase inhibitors and memantine are the only drugs approved by the US Food and Drug Administration for its treatment. These drugs provide symptomatic treatment but do not alter the course of the disease. Hence the modern therapeutic options that target the disease modification part are on a rise. The multiple mechanisms involved in the pathogenesis of AD create considerable difficulty in producing an effective treatment (Fig. 1). This current review attempts to summarize the existing therapeutic

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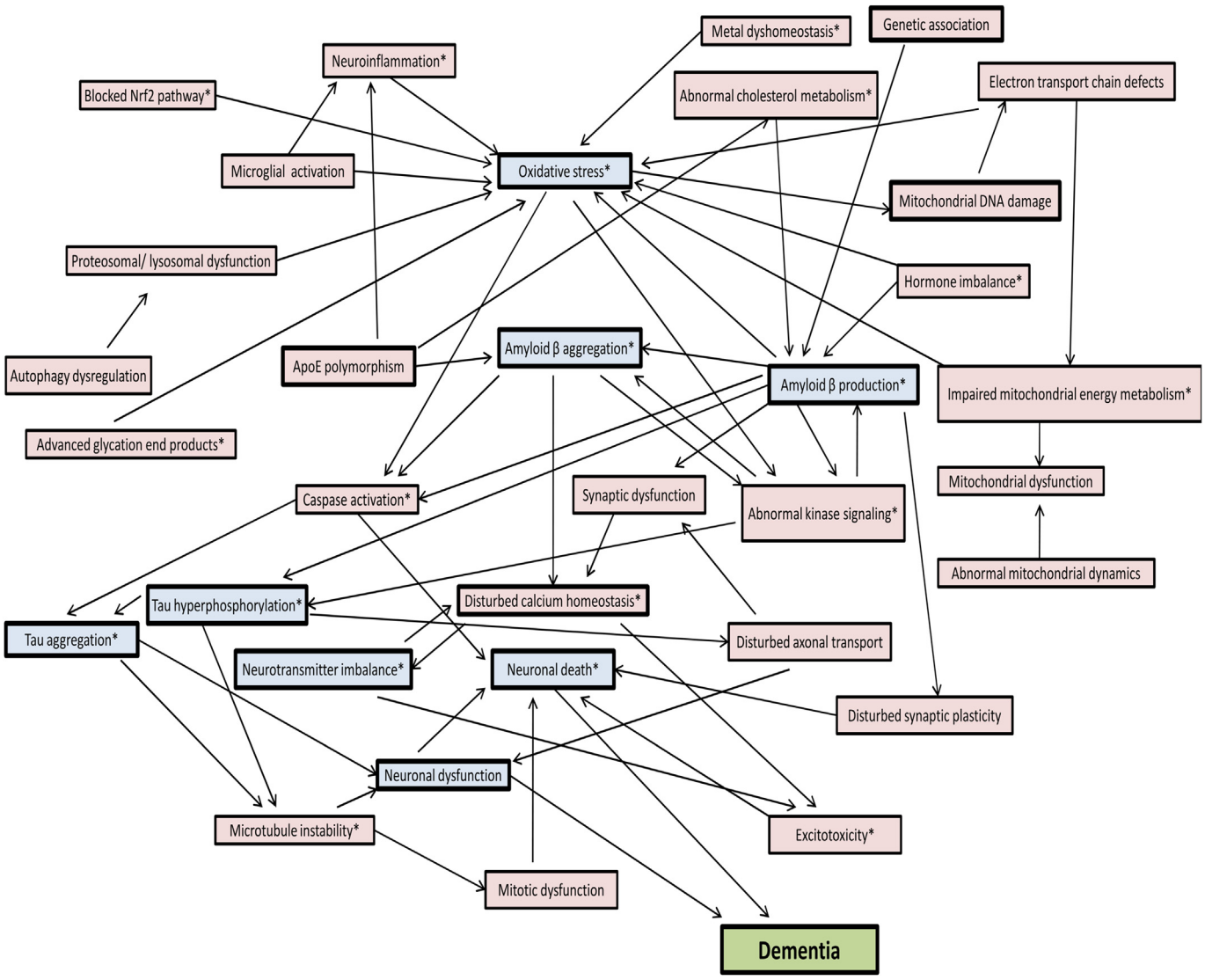

Fig. 1. Pathogenesis of Alzheimer's disease – Web of causation. The figure shows the various mechanisms involved in pathogenesis of Alzheimer's disease. The major mechanisms are in bold boxes. *Indicates the mechanisms against which therapeutic strategies are targeted.

strategies till date with correlation to the pathophysiologic mechanisms for AD (Table 1).

2.1. Modulating neurotransmission

The cholinergic group of neurons is the main neurotransmitter system involved in AD and basal forebrain cholinergic loss is a well recognized pathology. These neurons maintain cortical activity, cerebral blood flow, modulate cognition, learning, task and memory related activities, development of the cerebral cortex and regulation of sleep–wake cycle (Berger-Sweeney, 2003; Schliebs and Arendt, 2006). Considering the many functions of the cholinergic neurons, the symptom complex in AD can at least be partially understood.

The dysfunction of the cholinergic system in AD occurs at various levels including a decreased choline acetyltransferase activity, reduced choline uptake, a decrease in acetylcholine synthesis (Slotkin et al., 1990) and altered levels of acetylcholine receptors (AChRs) (Xu et al., 2012). Glutamate is the primary excitatory neurotransmitter in the hippocampal and neocortical regions of the brain, and they do play a significant role in cognition, learning and memory process. The post-synaptic membrane has high density of one of its receptors- the N-methyl-D-aspartate (NMDA) receptor. Studies have shown there is an extracellular glutamate excess in AD, contributed both by an increased presynaptic glutamate release and decreased re-uptake which, in turn lead to a tonic activation of NMDA receptors (Revett et al., 2013). The excitotoxicity is 'slow' in contrast to the acute or rapid form that occurs with stroke or epilepsy. Impaired insulin signaling along with mitochondrial dysfunction and receptor abnormalities (Beal, 1992) can predispose to this process when glutamate is excitotoxic even at physiological concentrations (Novelli et al., 1988). Dysfunction in other neurotransmitter systems such as γ-aminobutyric acid (GABA), histamine, and serotonin systems of neurons also lead to AD. The modulation of neurotransmission with drugs continue to remain the best approach to providing symptomatic improvement in patients; of late, mechanistic insights into their disease modifying aspects have also been highlighted.

2.1.1. Cholinesterase system

The four acetylcholinesterase inhibitors (AChEI) approved by the U.S. Food and Drug Administration for the treatment of AD are