Neuroscience and Biobehavioral Reviews 73 (2017) 340–358

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review article

Neurophysiological assessment of neural network plasticity and connectivity: Progress towards early functional biomarkers for disease interception therapies in Alzheimer's disease

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ARTICLE INFO

Article history:
Received 25 July 2016
Received in revised form 4 November 2016
Accepted 16 December 2016
Available online 24 December 2016

ABSTRACT

Despite a great deal of research into Alzheimer's disease (AD) over the last 20 years, an effective treatment to halt or slow its progression has yet to be developed. With many aspects of the disease progression still to be elucidated, focus has shifted from reducing levels of amyloid β (Aβ) in the brains of AD patients towards tau, another pathology, which initiates much earlier in deeper brainstem networks and is thought to propagate via cell-to-cell processes prior to the onset of amyloid pathology and cognitive impairments. In-vitro, ex-vivo molecular biology/biochemistry read-outs, and various transgenic animal models have been developed, yet clinical failures have highlighted a clear disconnect and inadequate use of such animal models in translational research across species. AD pathology is now estimated to begin at least 10–20 years before clinical symptoms, and imaging and cerebrospinal fluid biomarkers are leading the way in assessing the disease progression at a stage where neuronal damage has already occurred. Here, we emphasize the relevance of assessing early disruptions in network connectivity and plasticity that occur before neuropathological damage and progressive memory dysfunction, which can have high translational value for discovery of pre-symptomatic AD biomarkers and early mechanism-based disease interception therapeutics.

Contents

Abbreviations: Aβ, amyloid Beta; ACh, acetylcholine; AChEI, acetylcholinesterase inhibitor; ACH, amyloid cascade hypothesis; AD, Alzheimer's disease; APP, amyloid precursor protein; ARIA-E, amyloid related imaging abnormalities related to edema; CSF, cerebrospinal fluid; EEG, electroencephalogram/electroencephalography; EROS, event-related oscillations; ERP, event-related potentials; fAD, familial Alzheimer's disease; fMRI, functional MRI; FTDP-17, frontotemporal dementia and parkinsonism linked to chromosome 17; LC, locus coeruleus; LTP, long-term potentiation; MAOI, monoamine oxidase inhibitor; MCI, mild cognitive impairment; MEG, magnetoencephalography; NA, noradrenaline; PDGFB, platelet derived growth factor B; PET, positron emission tomography; PP2A, protein phosphatase 2A; PS, presenilin; pTau, phosphorylated tau; sAD, spontaneous Alzheimer's disease.

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http://dx.doi.org/10.1016/j.neubiorev.2016.12.020
0149-7634/

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease and is the cause of approximately 60–80% of dementia cases (Alzheimer's Association, 2015). Symptoms include impairments in cognitive function and loss of memory, which increase in severity over the progression of the disease. In the late stages of the disease, loss of motor skills such as swallowing and walking result in a complete loss of independent living. Two hallmark lesions are found in the brains of AD patients: extensive extracellular plaques of amyloid beta (Aβ) and intracellular neurofibrillary tangles made up of hyperphosphorylated tau protein. Additionally, AD brains also present with severe neurodegeneration and widespread neuroinflammation. This multifactorial nature of AD has made determining the direct impact of each individual factor to the overall disease state very difficult.

AD is primarily a disease of the elderly; most people who are diagnosed are aged 65 or older (Alzheimer's Association, 2015). Increases in life expectancy coupled with decreases in fertility have resulted in an ageing global population (United Nations Department of Economic and Social Affairs, 2015). It has been predicted that in the next ten years, for the first time in history, over 65's will outnumber children under 5 (US Census Bureau, 2009). There are currently an estimated 46.8 million people living with dementia worldwide, a number which has been predicted to double every 20 years (Prince et al., 2015). Currently there are no drugs available which stop or slow the progression of Alzheimer's disease, and only 4 compounds have been licensed to alleviate cognitive impairments. AD is a rapidly growing public health problem that, without any available treatment to slow its progression, will continue to grow unchecked.

A review of completed clinical trials for 244 AD compounds between 2002 and 2012 found an overall success rate for approval was 0.4%, among the lowest for any therapeutic area (Cummings et al., 2014), including some high profile, costly late stage failures (Table 1). The aim of this review is to address the recent stagnation in AD drug discovery, explore some recent developments in Alzheimer's research and their implications for possible therapeutics. Finally, the review will cover some of the important considerations in translating preclinical breakthroughs into clinical success.

2. AD and Aβ

2.1. Amyloid cascade hypothesis

In 1907, in a post mortem analysis of the brain of a severely demented 51 year old woman, Alois Alzheimer described "peculiar bundles of fibrils", and "miliar foci of a peculiar matter", distributed throughout the cortex (Alzheimer, 1907; Strassnig and Ganguli, 1987). This was the first clinical recognition of the senile plaques and neurofibrillary tangles of what would later be described as Alzheimer's disease. It was not until the mid-1980's when the main components of these lesions, amyloid beta and tau protein, respectively, were identified (Glenner and Wong, 1984; Kosik et al., 1986). Soon after, it was discovered that a mutation in the gene for amyloid precursor protein (APP) on Chromosome 21 could cause familial Alzheimer's disease (fAD) (St George-Hyslop et al., 1987). APP is cleaved by γ-secretase to produce Aβ (Kopan and Ilagan, 2004). This also explained the common occurrence of AD in Downs Syndrome, a genetic disorder caused by an extra copy of chromosome 21 (Jacobs et al., 1959; Lejeune et al., 1959). This led to formulation of the Amyloid Cascade Hypothesis (ACH) by (Hardy and Higgins, 1992), a hypothesis which would go on to shape AD research and drug discovery.

The ACH posits that an accumulation of Aβ, as a result of increased production or reduced clearance, causes a cascade of neurodegenerative processes including synapse loss, inflammation and neurodegeneration (Hardy and Higgins, 1992). Importantly, this hypothesis places tau pathology as a downstream effect of amyloid pathology, and suggests that Aβ accelerates the formation of neurofibrillary tangles. This attractive hypothesis considered both genetic and biochemical factors, and provided the pharmaceuticals industry with an appealing target; by reducing levels of amyloid beta in the brain, the progression of AD could be slowed or halted. In the following years, both research and industry turned their focus to this target; between 2002 and 2012, 65% of the clinical trials for AD modifying agents targeted Aβ, yet all have failed so far (Cummings et al., 2014). Although these failures are not the main focus of this review, we will briefly cover some notable examples, some possible reasons for their lack of success, and the consequences of these failures.

2.2. Aβ – example therapeutic strategies

There have been a number of different approaches to reducing levels of Aβ in the brain. One compound, Semagacestat, was shown to inhibit γ-secretase, theoretically reducing production of Aβ (Kopan and Ilagan, 2004). Preclinical data demonstrated reductions in cerebrospinal fluid (CSF) Aβ (Hyslop et al., 2004), but no reductions in levels of plaques. Phase 2 clinical trials showed that while Aβ production could be effectively inhibited, cognitive function, as measured by ADAS-cog, was worsened (Fleisher et al., 2008). Additionally, it was shown that the dosage was limited by side effects, such as rashes and changes in hair colour. These side effects were suggested to result from alterations in Notch