Journal of Alzheimer's Disease 101 (2024) S1–S2
DOI 10.3233/JAD-249016
IOS Press

Preface

Therapeutic Trials in Alzheimer's Disease: Where Are We Now?

Alzheimer's disease (AD), the most common form of dementia among older adults, is still a major scientific and clinical challenge, particularly regarding its early diagnosis and treatment. Over decades, significant efforts have been made to find the cause(s), pathogenic mechanisms, biomarkers for the early detection, and treatment of AD. Based on the growing knowledge about the multiple mechanisms involved in AD pathophysiology, many therapeutic interventions have been developed to target pathological events that are believed to play a crucial role in the course of the disease. Theoretically, those therapeutic interventions have the potential to stop or at least slow down structural and functional brain alterations providing sustainable improvements in cognitive function.

Over the past three decades, researchers have mainly focused on approaches aimed to decrease amyloid-β, considered by many as the cause of AD. However, those therapies failed due to lack of clinically meaningful efficacy and/or to serious side-effects. Nevertheless, those studies generated data that helped in the creation of new anti-amyloid treatments. On the other hand, the failure of those therapies led many researchers to explore the efficacy of strategies aimed at tackling other players in AD pathophysiology or its risk factors.

This book, which is divided into 6 parts, discusses the past and present clinical trials in AD based on pharmacological and non-pharmacological/lifestyle strategies, with varying degrees of success.

Part 1 focusses on pharmacological strategies aimed at the two proteins associated with AD, amyloid-β and tau. The therapeutic effects of amyloid-β and tau immunotherapies, which modulate the immune system response to the presence of these two proteins, are discussed. The effects promoted by the inhibitors of β-secretase (BACE), a critical enzyme involved in amyloid-β biosynthesis, and of glutaminyl cyclase, which is responsible for the formation of the toxic pyroform of amyloid-β are also debated. The therapeutic efficacy of CT1812, a small-molecule antagonist of the sigma 2 receptor, which reduces the affinity of oligomeric amyloid-β for neuronal receptors, interfering with Aβ-induced synaptic toxicity, is also discussed. Part 1 finishes discussing the ameliorative effects associated with the inhibition, promoted by Leucettinib-21, of the tyrosine phosphorylation-regulated kinase-1A (Dyrk1a), which phosphorylates the amyloid-β precursor protein and tau.

Besides amyloid-β and tau proteins, several other therapeutic targets for AD have been identified.

Part 2 of the book is devoted to discussing a broad range of therapeutic strategies including metal-targeting agents and antioxidants since metals toxicity and oxidative stress are interlinked and consistent features of AD. Moreover, the potential efficacy of CMS121, a flavonoid fisetin-derivative that targets oxytosis/ferroptosis, is discussed. The ameliorative effects promoted by molecules aimed at improving sleep and, consequently, cognition are also debated. The modulation of AD pathophysiology by phytoestrogens and hormone therapy is also approached in part 2.

Part 3 deals with repurposed drugs, particularly antidiabetics and lipid lowering-therapies due to the similarities found between type 2 diabetes and AD and the connection found between excessive levels

ISSN 1387-2877/$35.00

of triglycerides and cholesterol and increased risk of developing AD, respectively.

The challenges, advances, and therapeutic effects of stem cells and gene therapies for AD are detailed and discussed in part 4 of the book.

Part 5 debates the therapeutic effects of non-pharmacological approaches particularly of specific diets, namely ketogenic diets, and omega 3 and nicotinamide adenine dinucleotide (NAD^+) supplements as well as the benefits promoted by physical exercise, yoga, and acupuncture.

Finally, part 6 of the book discusses the benefits promoted by brain stimulation, a technique that modulates brain activity. Additionally, the crucial usefulness of several imaging techniques (positron emission tomography, computed tomography, magnetic resonance imaging) is discussed, putting the focus on their ability to assess the response of demented individuals to treatments.

We are very grateful to the contributors for bringing their expertise and perspectives to these topics.

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