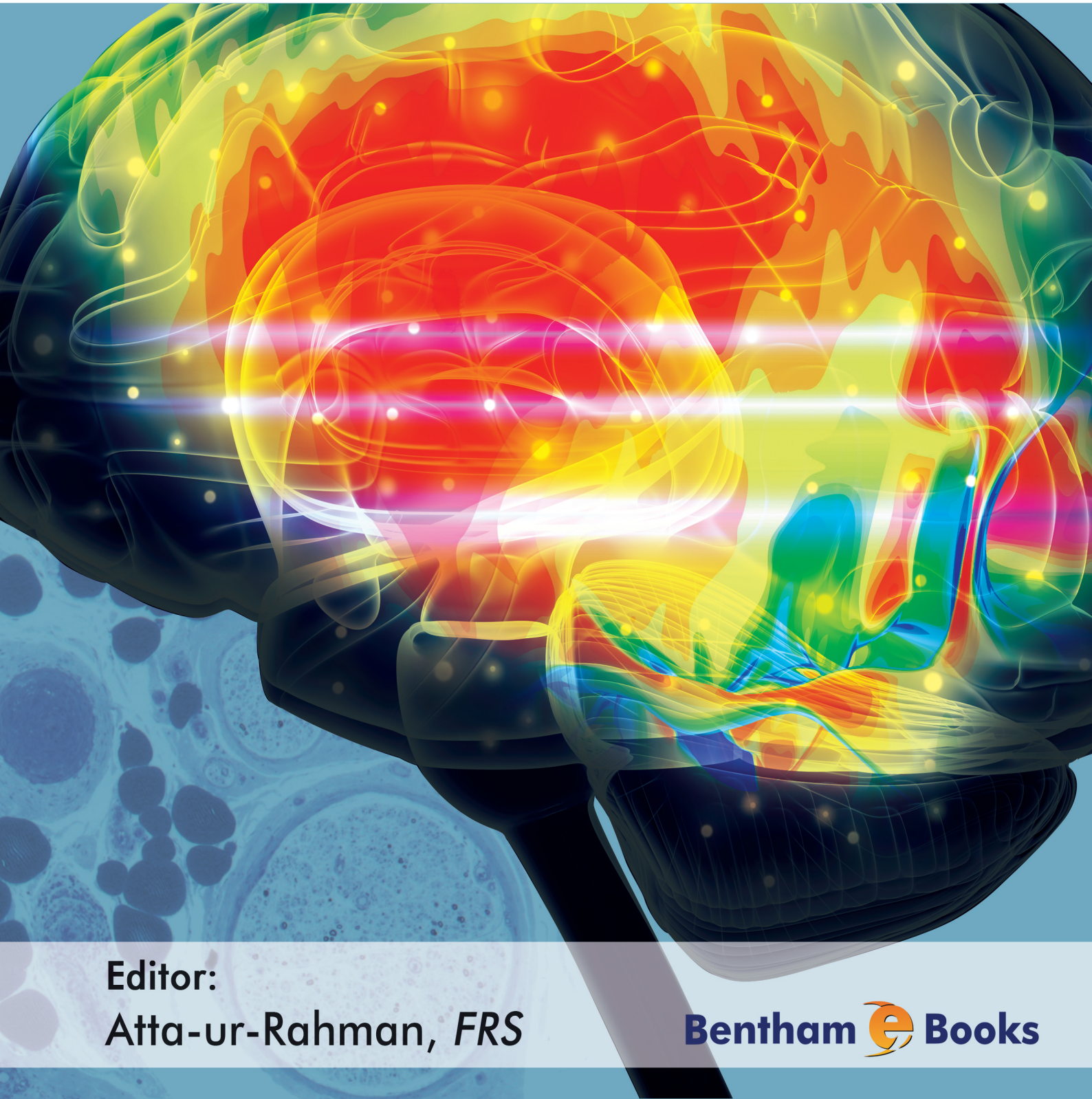
eISBN: 978-1-68108-231-8
ISBN: 978-1-68108-232-5

eISSN: 2214-5168
ISSN: 2451-8743

Frontiers in Clinical Drug Research (Alzheimer Disorders)

Volume 5



Editor:
Atta-ur-Rahman, *FRS*

Bentham Books

Frontiers in Clinical Drug Research

Alzheimer Disorder

(Volume 5)

Edited By

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Frontiers in Clinical Drug Research - Alzheimer Disorders

Volume #5

ISSN (Online): 2214-5168

ISSN (Print): 2451-8743

Editors/Authors: Prof. Atta-ur-Rahman, *FRS*

ISBN (Online): 978-1-68108-231-8

ISBN (Print): 978-1-68108-232-5

First published in 2016.

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CONTENTS

PREFACE

The book series, "***Frontiers in Clinical Drug Research – Alzheimer Disorders***" presents some important advancements in the field in the form of cutting edge reviews written by eminent experts.

Chapter 1 by Paul David Dash discusses the significant impact of cognitive impairment on a number of clinical matters. The author briefly explains the pros and cons of some of the numerous cognitive screens that can be utilized for screening purposes.

Chapter 2 Zaciragic *et al.* discuss the detrimental vascular changes that lead to consequent amyloid- β accumulation. This in turn leads to dementia. Moreover it provides a comprehensive insight into currently available evidence on molecular pathways and factors implicated in the above mechanisms. The findings from ongoing clinical trials and results from studies using novel pharmacological approaches to target endothelial dysfunction and chronic low-grade inflammation as pathophysiological events that contribute to the onset and development of dementia disorders are summarized.

Choo & Grubman in chapter 3 present an update on the prevailing mechanistic hypotheses, to explain AD pathogenesis, including the cholinergic, amyloid-cascade, inflammatory and metal dyshomeostasis theories. They present the recent clinical developments in therapies targeting each of the hypotheses, and highlight promising areas requiring further attention.

In chapter 4, Mareii *et al.* highlight the recent thinking against the long standing amyloid cascade hypothesis as well as the major efforts in the experimental application of stem cell based therapies used as treatment options for AD. Demarin *et al.*, in chapter 5 emphasize on the early disease detection and delaying cognitive impairment via various lifestyle modifications.

In chapter 6, Matei *et al.* present the methods of extraction, identification and quantification of the active compounds from various vegetal products *e.g.* curcuminoids, ellagic acid, gallic acid, salvianolic acid B, resveratrol and epicagallocatechin-3-gallate that can target the causative agent of Alzheimer's disease.

The 5th volume of this book series represents the results of a huge amount of work by many eminent researchers. I am grateful to the authors for their excellent contributions. I would also like to express my gratitude to the editorial staff of Bentham Science Publishers, particularly Mr. Mahmood Alam (Director Publication), Mr. Shehzad Naqvi (Senior Manager

Publications) and Ms. Fariya Zulfiqar (Assistant Manager Publications) for their hard work and persistent efforts.

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CHAPTER 1

Should Physicians Screen for Dementia in the Primary Care Setting?

Paul David Dash*

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Abstract: The question of possible benefits of physicians screening for dementia in elderly patients in the outpatient setting remains open. Although no controlled studies have thus far been able to conclusively demonstrate that doing so is in fact beneficial, the end points of such studies, such as mortality, are rather crude. Increasingly, there are arguments that harder to track end points need to be examined in more detail, and that earlier recognition of cognitive impairment can potentially have a significant impact on a number of clinical matters. These include, for example, recognition of potential problems with medication compliance, driving risk, predicting post-operative delirium, and allowing more time for patient and family planning of finances and living arrangements, as well as recommending life style changes in diet and exercise habits that may help retard the progression of early cognitive impairment. In this article we will discuss evidence regarding these points, and also give a brief outline of the pros and cons of some of the numerous brief cognitive screens that can be utilized for screening purposes.

Keywords: Alzheimer's, Dementia, Delirium, Prevention, Screening.

INTRODUCTION

This article addresses a central question: can screening for dementia make a meaningful difference in patient care and outcomes? There are several components to this question. What makes up a "meaningful difference" in patient

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Atta-ur-Rahman (Ed.)

care? What makes up a "meaningful difference" in patient outcome? What patient outcomes are we talking about exactly? For example, not only longevity, but also quality of life for the patient and caregiver, and intangible outcomes such as better ability for the patient and family to plan for the future must be taken into account and may be difficult or even impossible to quantify. Another question before deciding to proceed with dementia screening is whether its benefits outweigh the risks. For example, a false positive screen can lead to costly additional testing and unnecessary anxiety. An additional question, if we decide in favor of screening for dementia, is what instruments to use as the screening tools. (We should note that we may use Alzheimer's and dementia somewhat interchangeably in this article; Alzheimer's disease is of course the most common cause of dementia in the elderly, and some studies take steps to try to exclude other forms of dementia).

Several reviews on this topic have been published previously. In 2003, the US Preventive Service Task Force published its review, with the conclusion that there was not enough evidence to support routine dementia screening [1]. Subsequently, a work group convened by the Alzheimer's Foundation of America and the Alzheimer Drug Discovery Foundation in 2011, which included the lead author in the 2003 study, argued that screening could be helpful in improving dementia detection and treatment [2]. Some of the same authors including myself have also argued previously for the value of dementia screening, pointing out several of the possible advantages discussed in detail below [3].

Screening for a disease can happen at the population or individual level. Examples of population screening include national level decisions to do mass screenings of subpopulations for a disease, such as mammography for women over a certain age for breast cancer, or colonoscopies for those over 50 for colon cancer. Individual level screening, also known as case finding, occurs at the individual patient-physician level. Examples include routine blood pressure checks at every doctor visit, or somewhat more controversially, PSA screening for older men. The focus here is on identifying existing disease in those who don't know they have it. This article is concerned only with the case finding level of screening, as the title implies.

SECTION 1: SHOULD WE SCREEN FOR DEMENTIA?

Considerations in Screening for a Disease

Before we even get to the question of screening for dementia specifically, we need to consider generally what makes a disease worth screening for, and see whether dementia fits into that category. There are several obvious and not so obvious criteria for a disease to be considered worth screening. Although detailed criteria for screening have been developed by WHO (the Wilson criteria in 1968[1], and subsequently revised in 2008[2]), in my opinion the following simplified considerations are among the most important:

1. The disease should be prevalent and costly enough to make screening for it worthwhile;
2. Early stages of the disease should not be obvious, such that a screening tool to uncover it is necessary;
3. The screening tool should not be overly costly in terms of expense and physician time and must be reasonably effective;
4. The potential harm in a false positive or false negative diagnosis *via* screening does not outweigh the net benefit (which includes potential benefits from a true negative diagnosis as well as the true positives). "Harm" can reflect medical costs, such as those incurred by getting other tests in pursuit of a screen testing, as well as human suffering and other intangibles;
5. Making an earlier diagnosis actually makes a difference in disease outcome compared to later diagnosis. Obviously this is the key question.

These factors can interplay with one another. For example, on the population screening level, phenylketonuria is rare, but the screening is cheap and the treatment effective, so it along with some other rare metabolic diseases are routinely checked in newborns. On the other hand, even if earlier treatment makes only a small difference, for a common disease with inexpensive screening tests it may still be worthwhile to screen. Of course, the precise econometric values for earlier intervention savings may be impossible to quantitate. As we shall see, dementia qualifies easily on the first four criteria, but arguments persist about the fifth. That makes the decision to screen worthy of further discussion.

CHAPTER 2

Endothelial Dysfunction and Chronic Low-Grade Inflammation as Potential Therapeutic Targets in Dementia Disorders

Asija Zaciragic[1,*], Nesina Avdagic[1], Nermina Babic[1], Amela Devisevic[1], Amina Valjevac[1], Almir Fajkic[2], Jasminko Huskic[1], Almira Hadzovic-Dzuvo[1] and **Orhan Lepara[1]**

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Abstract: The inability of drugs based on the amyloid-clearing strategies to provide benefits for Alzheimer's disease (AD) patients has led to widely accepted notion that the paradigm in dementia research should be broaden beyond amyloid deposition and clearance. In recent years significant overlap between cardio-metabolic risk factors and cognitive decline has been reported. Consistent with these observations, the importance of endothelial dysfunction in the development of AD has been highlighted. According to newly proposed "vascular hypothesis" for AD development, vascular risk factors lead to blood–brain barrier (BBB) dysfunction and a reduction in the cerebral blood flow. These two detrimental vascular changes result in the reduction of amyloid-β clearance as well as in its increased production leading to consequent amyloid- β accumulation. The increase in amyloid-β leads to neuronal dysfunction and injury causing cognitive dysfunction and neurodegeneration with consequent dementia. Furthermore, a growing body of evidence also suggest that the impaired structure and function of cerebral blood vessels and cells in AD patients is mediated by vascular oxidative stress as well as by chronic low-grade inflammation. The importance of inflammatory changes in many age-related diseases including dementia has led to

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Atta-ur-Rahman (Ed.)

coining and use of the term “inflammaging” to indicate that ageing is accompanied by a low-grade chronic up-regulation of certain pro-inflammatory responses.

The aim of this chapter is to provide a comprehensive insight into currently available evidence on molecular pathways and players implicated in the above mechanisms. Furthermore, chapter summarizes findings from ongoing clinical trials and results from studies using novel pharmacological therapeutics targeting endothelial dysfunction and chronic low-grade inflammation as pathophysiological events that contribute to the onset and development of dementia disorders.

Keywords: Alzheimer's disease, Alzheimer's disease clinical trials, Cardio-metabolic risk factors, Chronic low-grade inflammation, Cognitive decline, Cytokine suppressive anti-inflammatory drugs, Dementia disorders treatment, Endothelial dysfunction, Endothelin receptor antagonists, Inflammaging, Nonsteroidal anti-inflammatory drugs.

INTRODUCTION

Prevalence of dementia significantly increases with age and Alzheimer’s disease (AD) accounts for up to 75% of cases. AD represents neurodegenerative disorder that affects nearly 2% of the population in industrialized countries [1]. Based on a data from 2010, AD affects 25 million people worldwide [2]. Since advanced age is the most significant risk factor for AD, medical and other kinds of costs of this disease cannot be overlooked. AD has enormous impact worldwide on the affected individuals, caregivers and overall public health care system. Individuals suffering from AD have significantly shortened life expectancy, their quality of life is drastically decreased and in many cases they require institutionalization caused by their physical disability. Studies have shown that AD patients have two-to fivefold increased risk of death and median survival time for newly diagnosed AD patients is from 3 to 6 years. Shorter survival is often reported for those AD patients that have poorer cognitive function, low education level, and comorbidities such as heart disease, hypertension and diabetes. Furthermore, white race, older age and male sex are associated with shorter life expectancy in individuals that suffer from AD [3]. Alzheimer’s Association data from 2009 have revealed that in the US the annual costs for patients with AD and other forms of dementia were estimated to be US$148 billion plus US$94 billion of unpaid care

service [4]. Having in mind progressive nature of AD and a fact that its adequate treatments are still lacking, this disease represents tremendous burden for family members and overall society since AD patients require permanent care and therapy. At present there are no treatments that can stop or reverse neuro-degeneration typical for AD. However, better understanding of AD etiology and pathophysiology will lead to the discovery of effective preventive and therapeutic approaches that will reduce incidence and improve treatment of AD.

Pathogenesis of AD is multifactorial and yet fully unknown. Known risks factors for AD include age, genetic, environmental, vascular, life-style factors and low educational income. This disease is neuropathologically characterized by presence of neurofibrillary tangles and senile neuritic plaques, amyloid-β peptid deposits and widespread neuronal loss. Main symptoms of AD are cognitive decline, memory loss, altered behavior and language deficit. As they progress in time, these symptoms lead to severe impairment in daily functioning and in later stages AD patients require total care [5].

AD is often preceded by 'mild cognitive impairment' (MCI). By widely accepted definition MCI represents a transitional state between normal aging and developed dementia. It is characterized by greater cognitive decline then expected for the age of the affected individuals but with still preserved activities of daily functioning. Between 3% and 19% of adults over the age of 65 suffer from this condition, and according to current evidence more than a half of individuals with MCI will develop dementia within 5 years [6, 7]. Significant efforts are made in early diagnosis of this condition and in its proper pharmacotherapy so that development of dementia in MCI suffering patients is prevented.

As there is yet no reliable peripheral biochemical marker for the AD, definitive diagnosis of AD can only be confirmed by postmortem examination of the brain that must contain sufficient number of plaques and tangles. Extracellular deposits of fibrils and amorphous aggregates of amyloid β-peptide (Aβ) form plaques, and intracellular fibrillar aggregates of the microtubule-associated protein tau which exhibit hyperphosphorylation and oxidative modifications form neurofibrillary tangles. Plaques and tangles are present mainly in brain regions involved in learning, memory and emotional behaviors such as the entorhinal cortex, hippo-

CHAPTER 3

Recent Clinical Developments in Alzheimer's Disease

Xin Yi Choo* and **Alexandra Grubman**

Department of Pathology, The University of Melbourne, Victoria, Australia

Abstract: Alzheimer's disease is the most common neurodegenerative disease. Despite intensive research, promising therapies have failed to translate to the clinic. This chapter will review the prevailing mechanistic hypotheses to explain AD pathogenesis, including the cholinergic, amyloid-cascade, inflammatory and metal dyshomeostasis theories, present an update on the clinical developments in therapies targeting each of the hypotheses, and highlight promising areas requiring further research.

Keywords: Alzheimer's disease, Amyloid antibodies, Amyloid cascade hypothesis, Cholinergic hypothesis, Clinical trials, COX inhibitors, Familial, Metal homeostasis, Metal ionophores, Multi-targeting, Neuroinflammation, Secretase modulators, Sporadic.

INTRODUCTION

Alzheimer's disease (AD) is the most common neurodegenerative disease (NDD), with age being the most common risk factor [1]; it is expected to affect 1 in every 85 people worldwide by 2050 [2]. The clinical symptoms of AD include progressive cognitive and functional impairment [3]. AD is classified into two broad categories. Sporadic late onset AD (LOAD), usually occurring after the age of 65, accounts for greater than 95% of AD cases [4], while early onset AD (EOAD), which occurs before the age of 65, accounts for the remaining AD

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Atta-ur-Rahman (Ed.)

occurrences (<5%) [4, 5]. Early onset familial AD (EOFAD), caused by mutations in the presenillin-1 (*PSEN1*), presenillin-2 (*PSEN2*) or amyloid precursor protein (*APP*) genes accounts for 1-2% of AD cases [6, 7]. The remaining 3-4 % of AD patients The remaining 3-4 % of AD patients are expected to carry an undetermined deterministic mutation that causes the early disease onset [6]. In contrast, the presence of ε4 allele (ApoE4) of apolipoprotein E (*APOE*) has been recognised as a major genetic risk factor for LOAD [8]. Pathological hallmarks of AD are comprised of accumulation of extracellular amyloid-beta (Aβ) plaques, the presence of intracellular neurofibrillary tangles (NFT) composed of hyperphosphorylated microtubule associated protein Tau, and brain atrophy of the hippocampal and neocortical regions as a result of neuronal and synaptic loss [9]. Other established pathologies associated with AD include oxidative stress-induced damage, neuroinflammation and bio-metal dyshomeostasis (see [10 - 12] for reviews).

Although extensive research has helped to better understand the disease, the aetiology of AD has remained indistinct. This lack of knowledge greatly impedes the progress of diagnostic advancements and drug development. The gold standard for AD diagnosis is through post-mortem brain autopsy verification of disease histopathology [13]. Besides cases with detectable genetic mutations, clinical diagnosis of probable AD is carried out using criteria-based approaches [13 - 16], taking into account factors such as cognitive and behavioural performance, biological evidence and exclusion criteria. Increasingly, it is recognised that neuropathological changes can occur over long periods before patients begin to display clinical symptoms of AD [15, 17]. As such, this asymptomatic preclinical stage of disease is viewed as the golden opportunity for early therapeutic intervention. Unfortunately, with the lack of biomarker(s) that can accurately predict progression to AD and the lack of effective therapeutic options, early targeting is currently unavailable as a therapeutic approach. Interestingly, transcriptome analysis of post-mortem tissues from cognitively normal control patients, mild cognitive impairment (MCI) patients and AD patients, suggest that distinct changes in expression of genes relating to synaptic function [18 - 20], energy metabolism [18, 20] and inflammation [21, 22] occur in advance of progression to pathological stage of AD. Transcriptional changes

relating to aging and AD were also observed in young 3xTg-AD mice prior to developing AD phenotype [23]. These suggest pathways that can be explored as early targets for therapeutic intervention in AD.

Several different disease hypotheses have been generated to attempt to explain the origin of AD. Parallel with the development of the various hypotheses, proponents of individual hypotheses have also investigated therapeutic strategies targeted at the individual pathways predicted to be perturbed in AD. These strategies include targeting of the cholinergic system and other neurotransmitters, Aβ, NFT, neuroinflammation and bio-metal dyshomeostasis. To impede the rate of cognitive decline, early therapeutics mainly focused on targeting the central nervous system (CNS) to boost CNS functions. Aβ and NFT, popularly believed to drive AD progression, also became common targets for therapeutic intervention. With strong evidence demonstrating the detrimental role of neuroinflammation in propagating AD, anti-inflammatory therapeutics became widely adopted to curb damaging inflammatory processes. In recent years, with improved understanding of bio-metal deregulation in AD, novel strategies have targeted restoration of metal homeostasis. Nonetheless, out of over 150 therapeutics clinically tested in humans to date or currently in clinical trials, only 5 have been approved for use in the treatment of AD [24]. While the drugs currently approved for AD provide some symptomatic benefit, no available drug delivers a disease modifying effect, particularly for advanced stages of disease [25].

In this review, we will discuss the proposed mechanisms, as well as success and failure of therapeutic strategies developed in line with the (a) cholinergic hypothesis, (b) amyloid cascade hypothesis, (c) inflammatory hypothesis and (d) metal hypothesis in relation to AD. For comprehensive reviews of Tau and oxidative stress biology in AD and Tau-directed and anti-oxidant therapeutic strategies, refer [26] to and [27] respectively.

Therapeutic Strategies and Clinical Trials

Cholinergic Hypothesis

Although significant progress has been made in understanding the molecular mechanisms driving AD, most currently approved therapeutic strategies are still

CHAPTER 4

Recent Perspective About the Amyloid Cascade Hypothesis and Stem Cell-Based Therapy in the Treatment of Alzheimer's Disease

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Abstract: Alzheimer's disease (AD) is a complex neurodegenerative condition that is clinically characterized by impaired cognitive functions. The major morphologically observed lesion of AD encompasses the accumulation of extracellular amyloid aggregates (plaques) formed of amyloid-β (Aβ) protein and of intracellular neurofibrillary tangles (NFT) of hyperphosphorylated Tau protein. According to the currently accepted amyloid cascade hypothesis, the major induction factor underlying the loss of cholinergic neurons in the cortex and hippocampus is the pathological accumulation of a smaller protein fragments known as amyloid-β which in turn is derived from a larger membrane protein called amyloid precursor protein (APP). Based

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Atta-ur-Rahman (Ed.)

on this hypothesis, several diagnostic and drug-based therapeutic interventions were suggested, mostly targeting amyloid-β and hyperphosphorylated Tau proteins. Several data have emerged that might indicate the inconsistency of the amyloid cascade hypothesis. Moreover, due to the purely palliative nature of AD drugs used so far, new stem cell-based therapy has been suggested as a promising potential therapeutic approach. Several cell sources have been used, such as embryonic stem cells, neural stem cells, mesenchymal stem cells, and induced pluripotent stem cells. While this suite of cell-based trials has shown promising results in preclinical paradigms, stumbling blocks still exist in the current treatment regimens. The present review highlights the recent perspective that argues against the long standing amyloid cascade hypothesis as well as the major efforts in the experimental application of stem cell-based therapies used as treatment options for AD, and discusses the major impediments against their successful translation into clinical.

Keywords: Aβ42 peptides, Alzheimer's disease, Amyloidogenesis, Amyloid precursor protein (APP), Neuronal stem cells, Pathogenesis, Senile, plaques, Stem cells-Therapy.

ALZHEIMER'S DISEASE PATHOPHYSIOLOGY

Since the discovery of Alzheimer's disease (AD) in 1907, two major pathological AD associated proteins composed of amyloid β (Aβ), a small fragment of a larger precursor protein called amyloid precursor protein (APP) and a microtubule-associated intraneuronal tau protein have been incriminated as the major etiology underlying the massive loss of cholinergic neurons in the cortex and hippocampus of the brain [1 - 3]. Using Sephadex G-100 column chromatography, and by high performance liquid chromatography, a purified protein was derived from fibrils in cerebrovascular amyloidosis associated with Alzheimer's disease has been isolated. This protein have no homology with any protein sequenced, and may provide a diagnostic test for Alzheimer's disease and a means to understand its pathogenesis [4].

A monoclonal antibody to the microtubule-associated protein tau (tau) labeled some neurofibrillary tangles and plaque neurites, the two major locations of paired-helical filaments (PHF), in Alzheimer disease brain. [5].

Massive neuronal loss is associated with major synaptic losses reflected clinically

as gradual loss of recent memory functions and late-life dementia [6]. Based on the observed AD-associated pathology, the "amyloid cascade hypothesis," was proposed [7, 8]. Major evidence for this hypothesis included the discovery that mutations of APP genes are among the major genetic makeup of AD [9, 10].

During the last century, the amyloid cascade hypothesis represented the roadmap by which AD can be diagnosed and treated. Unfortunately, in most cases, this simple straightforward linear hypothesis failed to explain the complex biological and molecular pathways associated with the perplexing and devastating AD pathology. Smith *et al.* [11] stated that alternate interpretations of old data as well as new evidence indicates that amyloid-beta, far from being the harbinger of disease, actually occurs secondary to more fundamental pathological changes and may even play a protective role in the diseased brain. These findings bring into doubt the validity of the Amyloid Cascade Hypothesis as the central cause of Alzheimer disease and, consequently, the potential usefulness of therapeutic targets against amyloid-beta protein. This became more clear when many of Aβ and tau-protein-based preclinical and clinical trials failed to restore lost neuronal and cognitive functions associated with AD pathology [12, 13].

The palliative nature of AD drugs developed so far and the failure of amyloid and tau-based therapeutic protocols have prompted several investigators not only to point out the possible inconsistency of the amyloid cascade hypothesis, but also to start searching for novel non-drug based therapeutic protocols such as stem cell-based therapy [14]. In this respect, several cell sources have been used with the aim to provide an ample supply of suitable progenitor cells that might restore the lost neuronal and synaptic elements associated with AD [15, 16].

This review explores novel data that may modify or replace the amyloid cascade hypothesis, and presents major experimental findings relevant to stem cell-based therapy for AD.

GENERAL VIEW ABOUT AD

AD represents one of the major public health burdens in elderly population. The ratio of AD occurence is approximately one to nine in individuals of age < 65 year old and such figures worsen as the population of the world ages to approximately

CHAPTER 5

Current Concepts in Management of Alzheimer's Disease

Vida Demarin[1,*], Zlatko Trkanjec[2], Marijana Bosnar Puretić[2], Sandra Morović[3] and **Anton Glasnović[4]**

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Abstract: Alzheimer's disease (AD) is a neurodegenerative disease characterized by amyloid plaque and neurofibrillary tangles formation in the brain tissue. It is a progressive disease with death as the final outcome. In 2012 there were 35.6 million affected people worldwide and this number is constantly increasing. The main risk factor is age and life expectancy after the diagnosis is approximately ten years. The most important diagnostic procedures are neurocognitive tests, which are used to assess behavior and thinking abilities, while neuroimaging is used to exclude other brain pathologies and confirm the specific atrophic changes. Although a large number of studies have investigated this issue, no effective treatment for AD has been found. Most frequently used medications are ACh esterase inhibitors, mainly donepezil, rivastigmin and galantamine, and N-methyl-D-aspartate (NMDA) receptor antagonist, memantine, but they are mostly used to relieve the symptoms. Therefore, the emphasis should be put on early disease detection and delaying cognitive impairment through lifestyle modifications, such as increased physical activity, healthy nutrition, and mental training. The disease influences not only the patients' quality of life, but also that of the caregivers, and represents a heavy financial burden for the society as a whole.

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Atta-ur-Rahman (Ed.)

Keywords: ACh esterase inhibitors, Allopregnanolone, Alzheimer's disease, Amyloid, Bapineuzumab, Biomarkers, Canabinoids, Caregiver, Costs, Dementia, Diet, Dimebon, Herpes simplex virus, Immunotherapy, Insulin, Mild cognitive impairment, NMDA antagonists, PET, Statins, Tau protein.

INTRODUCTION

Alzheimer's disease (AD) is the most common form of neurocognitive impairment. It usually affects patients older than 65 years [1, 2], and when it is diagnosed in younger age groups it is referred to as early-onset AD. In 2012, there were 35.6 million affected people worldwide, and by 2050 this number is expected to increase to 1 in 85 people [3]. The disease was first described in 1906 by German physician Alois Alzheimer [1, 4]. He described the case of his patient Auguste D. who at the age of 40 experienced behavioral and memory changes, such as comprehension and memory impairment, dyslexia, dysgraphia, dysphasia, spatial disorientation, unpredictable behavior, paranoia and auditory hallucinations, psychosocial impairment, as well as insomnia. After her death at the age of 55, pathoanatomical examination showed a significantly reduced cerebral cortex with visible “miliary foci” (what is today called amyloid or senile plaques) and clumps and condensations of intracellular fibrils, which Alzheimer called “neurofibrillary degeneration” and are today known as neurofibrillary tangles [5].

EPIDEMIOLOGY

The incidence of AD is 5-8/1000, while that of all dementias is 10-15/1000. The most important risk factor for the development of AD is age – the risk doubles every five years after the age of 65 [7 - 9]. Women are at greater risk than men, especially after the age of 85 [10].

The prevalence of AD has doubled since the beginning of the 20th century, probably due an increase in life expectancy [6]. When analyzing the disease prevalence in particular countries we should take into consideration the mean age of the population, because less developed countries have shorter life expectancy [11 - 13].

SYMPTOMS AND DISEASE COURSE

AD develops slowly but progressively and the final outcome is death. Its progression is divided into four stages: preclinical, early, moderate, and advanced stage, with each stage being marked by further increase in cognitive and functional impairment [3, 14]. Diagnosis is usually established when symptoms start to affect patients' activities of daily life, while a few years before that, patients may experience mild cognitive impairment (MCI) [15]. MCI affects executive functions, such as attentiveness and abstract thinking, depression, apathy, irritability and reduced awareness of memory impairment [16 - 20]. There is still a dispute whether it corresponds to a different diagnostic category or it is in fact a preclinical stage of AD [21 - 22]. Early interventions can lead to significant delay in disease onset and symptom improvement, which is why emphasis should be put on disease prevention.

Early Stage

The first symptoms that lead to AD diagnosis are memory and learning impairment, while some patients develop more evident problems, such as language and executive functions impairment, and impairment of perception (agnosia) and movement execution (apraxia). Not all aspects of memory are equally impaired: episodic memory is less impaired than semantic memory, so major problems are reduced vocabulary and word fluency, both orally and in writing [16 - 18]. At this stage, the patient appropriately communicates basic ideas [18, 23], but frequently faces problems with fine motor tasks such as writing, drawing, dressing and planning of certain movements, Early symptoms often remain unnoticed or are misinterpreted as being related to the normal aging process.

Moderate Stage

With further disease progression, patients gradually lose their independence and become unable to perform most of the daily activities [16]. They experience reading, writing, and speech impairments, particularly in the form of paraphasias, *i.e.*, incorrect word substitutions [18, 23]. Also, impairments arise in the domain of complex motor actions and long-term memory [24]. Patients have a tendency to

CHAPTER 6

Natural Compounds from Plants Targeting Alzheimer's Disease

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Abstract: Alzheimer's disease is a common form of dementia. Drugs currently available for treatment of Alzheimer's disease are only symptomatic and act by augmenting the level of acetylcholine. These drugs do not stop or delay the evolution of disease and manifest specific adverse effects that limit their use. In this context, it is crucial the development of new drugs that will target the causal agent of disease. Such compounds that intervene at different levels in the pathogenesis of Alzheimer's disease were identified in plant extracts.

In this chapter, we propose an overview of some compounds that have anti-amyloidogenic activity of which the most important are: curcuminoids, ellagic acid, gallic acid, salvianolic acid B, resveratrol and epicagallocatechin-3-gallate. Besides the mechanism and biological actions, this chapter will present the vegetal products from which the active compounds are extracted, methods of extraction, identification and quantification. Selected techniques will be compared in terms of optimal conditions for extraction. Moreover, methods for identification and quantification will be described in terms of analytical conditions. Nature remains an important resource of active molecules and a hope in treating Alzheimer's disease.

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Atta-ur-Rahman (Ed.)

Keywords: Alzheimer's disease, Methods of extraction, Oxidative stress, Solvents, Vegetal products.

INTRODUCTION

Alzheimer's disease, named after the neurologist Alois Alzheimer (1864-1915) is a type of dementia characterized by a deterioration of mental capacity, which installs with age. Increasing life expectancy increases the risk of this disease.

Worldwide there are currently 24.3 million people with dementia and 4.6 million new cases are diagnosed annually. It is estimated that the number of people with dementia doubles every 20 years and for 2050 it is forecast to be 115 million people suffering from AD [1].

Hallmark brain abnormalities in AD are the formation of the senile plaques and neurofibrillary degeneration, processes that gradually causes the death of neurons, especially in the brain structures involved in cognitive processes such as frontal cortex, hippocampus, basal nucleus of Meynert [2].

Drugs currently available for treatment of Alzheimer's disease are only symptomatic and act by augmenting the level of acetylcholine, compensating for loss of cholinergic function: acetylcholine precursors, muscarinic agonist, nicotinic agonists and choline esterase inhibitors [2].

These drugs do not stop or delay the evolution of disease and manifest specific adverse effects that limit their use. In this context, the development of new drugs that will target the causal agent of disease is crucial.

Such compounds that intervene at different levels in the pathogenesis of Alzheimer's disease were identified in plant extracts.

In this chapter we propose an overview of the curcuminoids, ellagic acid, gallic acid, galagic acid salvianolic acid B, rosmarinic acid, punicallagin, resveratrol, epicagallocatechin-3-gallate, oleanolic acid, oleuropein, ginkgolide and biblobalide. These compounds act through diverse mechanisms in blocking the amyloid cascade: by stopping the aggregation of amyloid beta peptide and fibril formation, promoting the disaggregation of formed fibrils, inhibiting beta-

secretase and gamma-secretase or increasing alpha-secretase activity, thus increasing the production of non-amyloidogenic peptide.

Knowing that beta-amyloid peptide damages neurons by generating reactive oxygen species in the process of self-aggregation, the antioxidant activity of plant compounds must be taken into account as well. The majority of tests highlighting anti-amyloidogenic activities of natural compounds were performed *in vitro*, so further research is needed for confirmation of these activities *in vivo* and clinical trials for introduction of new drugs in therapy.

Besides the mechanism and biological actions, this chapter will present the vegetal products from which the active compounds are extracted, methods of extraction, identification and quantification. Selected techniques will be compared in terms of optimal conditions for extraction, such as solvents, modifiers used to improve the extraction, temperature, pressure and extraction time. Moreover, methods for identification and quantification will be described in terms of analytical conditions: derivatization of compounds, stationary and mobile phase, temperature, detector type, analysis time, limit of detection, limit of quantitation, correlation between the method/extraction solvent and the recovered concentration.

Knowing the different types of analysis methods that can be used for the extraction, separation, identification and quantification of proposed compounds is of great importance, the analysts can choose the most suitable and effective technical conditions, taking into account the available equipment.

Considering the fact that natural compounds have fewer side effects, are well tolerated and can be further used as models for the synthesis of novel drugs, nature remains an important resource of active molecules and a hope in treating Alzheimer's disease.

PATHOPHYSIOLOGICAL MECHANISMS

Beta-Amyloid and Tau Proteins

The best known pathophysiological mechanisms involved in AD are increased

SUBJECT INDEX

B

C

D

E

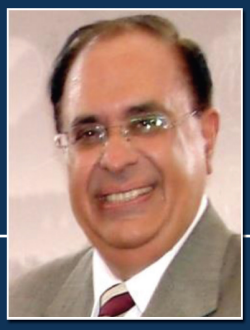
F

G

H

I

T



PROF. DR. ATTA-UR-RAHMAN, *FRS*

Prof. Atta-ur-Rahman obtained his Ph.D. in organic chemistry from Cambridge University (1968). He has 974 publications in several fields of organic chemistry including 718 research publications, 37 international patents, 151 books and 68 chapters in books published largely by major U.S. and European presses. He is the Editor-in-Chief of several European Chemistry journals and the Editor of "Studies in Natural Product Chemistry" 50 volumes of which have been published by Elsevier Science Publishers (Netherlands) under his Editorship during the last two decades. Eighty students have completed their Ph.D. degrees under his supervision.

Prof. Rahman was elected Fellow of Royal Society (London) (2006) and won the UNESCO Science Prize (1999). He has been conferred honorary doctorate degrees by Cambridge University and many other universities. He was elected Honorary Life Fellow of Kings College, Cambridge University (2007).