FRONTIERS IN CLINICAL DRUG RESEARCH - DEMENTIA

Editor:
José Juan Antonio Ibarra Arias

Bentham Books

Frontiers in Clinical Drug Research - Dementia

(Volume 2)

Edited by

Dr. José Juan Antonio Ibarra Arias
Centro de Investigación en Ciencias de la Salud (CICSA)
Facultad de Ciencias de la Salud Universidad Anáhuac
México Norte
Mexico

Frontiers in Clinical Drug Research – Dementia

Volume # 2

Editors: Prof. José Juan Antonio Ibarra Arias

ISSN (Online): 2717-5995

ISSN (Print): 2717-5987

ISBN (Online): 978-981-5039-47-4

ISBN (Print): 978-981-5039-48-1

ISBN (Paperback): 978-981-5039-49-8

need for a court order if at any point you breach any terms of this License Agreement. In no event will any delay or failure by Bentham Science Publishers in enforcing your compliance with this License Agreement constitute a waiver of any of its rights.

3. You acknowledge that you have read this License Agreement, and agree to be bound by its terms and conditions. To the extent that any other terms and conditions presented on any website of Bentham Science Publishers conflict with, or are inconsistent with, the terms and conditions set out in this License Agreement, you acknowledge that the terms and conditions set out in this License Agreement shall prevail.

Bentham Science Publishers Pte. Ltd.
80 Robinson Road #02-00
Singapore 068898
Singapore
Email: subscriptions@benthamscience.net

CONTENTS

PREFACE

Among neurodegenerative diseases, those that lead to a state of dementia are the aim of several investigations. Dementia is a chronic disease whose prevalence is increasing worldwide. The number of dementia patients in the world is approximately 50 million, and it is estimated that the number of patients will reach 131.5 million by 2050. This increase will be accompanied by a significant increase in medical expenditures and other expenses, especially for elderly patients. Therefore, the maintenance cost of dementia in the future is expected to be quite high. For this reason, several investigations aim, firstly, to describe the key mechanisms involved in the origin of dementia and, secondly, to establish preventive and/or therapeutic strategies in order to understand and mitigate this catastrophic pathology. This book aims to discuss the current comorbidities that cause cognitive impairment and the current management alternatives in cases of dementia for a better understanding of the current perspective on the subject.

The book contains five chapters that begin with a clear description of the comorbidities that induce mild cognitive impairment, continues with the description of some mechanisms that contribute to the development of dementia, and then moves on to the discussion of some encouraging therapies.

The editor would like to express his gratitude to the authors of the chapters presented in this book for their invaluable contributions.

Dr. José Juan Antonio Ibarra Arias
Centro de Investigación en Ciencias de la Salud (CICSA)
Facultad de Ciencias de la Salud Universidad Anáhuac México
University of Cambridge
Norte
Mexico

List of Contributors

Alejandra Romo	Centro de Investigación en Ciencias de la Salud (CICSA), Facultad de Ciencias de la Salud Universidad Anáhuac México, Norte, Mexico
Almudena Chávez-Guerra	Centro de Investigación en Ciencias de la Salud (CICSA), Facultad de Ciencias de la Salud Universidad Anáhuac México, Norte, Mexico
Antonio Ibarra	Centro de Investigación en Ciencias de la Salud (CICSA), Facultad de Ciencias de la Salud Universidad Anáhuac México, Norte, Mexico
Anamaria Jurcau	Faculty of Medicine and Pharmacy, Clinical Municipal Hospital, University of Oradea, Romania, Oradea
Adriane Bello Klein	Institute of Basic Health Sciences, Department: Physiology R. Sarmento Leite, Federal University of Rio Grande do Sul (UFRGS), CEP 90035-190- Porto Alegre, RS , Brazil
Alexandre Castro	Institute of Basic Health Sciences, Department: Physiology R. Sarmento Leite, Federal University of Rio Grande do Sul (UFRGS), CEP 90035-190- Porto Alegre, RS , Brazil
Alex Sander da Rosa Araujo	Institute of Basic Health Sciences, Department: Physiology R. Sarmento Leite, Federal University of Rio Grande do Sul (UFRGS), CEP 90035-190- Porto Alegre, RS , Brazil
Aziz Eftekhari	Russian Institute for Advanced Study, Moscow State Pedagogical University, 1/1, Malaya Pirogovskaya St, Moscow, 119991, Russian Federation Pharmacology and Toxicology Department, Maragheh University of Medical Sciences, Maragheh, Iran
Alex France Messias Monteiro	Postgraduate Program in Natural and Bioactive Synthetic Products, Health Sciences Center, Federal University of Paraíba, Castelo Branco Street, João Pessoa, PB – Brazil
Cumali Keskin	Medical Laboratory Techniques, Vocational Higher School of Healthcare Studies, Mardin Artuklu University, Mardin, Turkey
Daiane da Rocha Janner	Carlos Chagas Filho Institute of Biophysics – Neurogenesis Lab Av. Carlos Chagas Filho, Federal University of Rio de Janeiro (UFRJ) , 373–CEP 21941-902, Rio de Janeiro, RJ- Brazil
Elham Ahmadian	Kidney Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
Edeildo Ferreira da Silva-Júnior	Chemistry and Biotechnology Institute, Federal University of Alagoas, 57072-970, Maceió, AL – Brazil
Érika Paiva de Moura	Postgraduate Program in Natural and Bioactive Synthetic Products, Health Sciences Center, Federal University of Paraíba, Castelo Branco Street, João Pessoa, PB – Brazil
Francisco Jaime Bezerra Mendonça Júnior	Laboratory of Synthesis and Drug Delivery, State University of Paraíba, Horácio Trajano de Oliveira Street, João Pessoa, PB – Brazil

Herbert Igor Rodrigues de Medeiros	Postgraduate Program in Natural and Bioactive Synthetic Products, Health Sciences Center, Federal University of Paraíba, Castelo Branco Street, João Pessoa, PB – Brazil
Igor José dos Santos Nascimentos	Chemistry and Biotechnology Institute, Federal University of Alagoas, 57072-970, Maceió, AL – Brazil
Irada Huseynova	Institute of Molecular Biology & Biotechnologies, Azerbaijan National Academy of Sciences, 11 Izzat Nabiyev, Baku AZ 1073, Azerbaijan
Luciana Scotti	Postgraduate Program in Natural and Bioactive Synthetic Products, Health Sciences Center, Federal University of Paraíba, Castelo Branco Street, João Pessoa, PB – Brazil Teaching and Research Management, University Hospital of the Federal University of Paraíba, João Pessoa, PB – Brazil
Macarena Fuentes	Centro de Investigación en Ciencias de la Salud (CICSA), Facultad de Ciencias de la Salud Universidad Anáhuac México, Norte, Mexico
Maria Helena Vianna Metello Jacob	Montfort Hospital – Institut du Savoir 745, Montreal Road, Ottawa, ON K1K 0T1, Canada
Marcus Tullius Scotti	Postgraduate Program in Natural and Bioactive Synthetic Products, Health Sciences Center, Federal University of Paraíba, Castelo Branco Street, João Pessoa, PB – Brazil
Natan Dias Fernandes	Postgraduate Program in Natural and Bioactive Synthetic Products, Health Sciences Center, Federal University of Paraíba, Castelo Branco Street, João Pessoa, PB – Brazil
Roxana Rodríguez-Barrera	Centro de Investigación en Ciencias de la Salud (CICSA), Facultad de Ciencias de la Salud Universidad Anáhuac México, Norte, Mexico
Renad I. Zhdanov	Russian Institute for Advanced Study, Moscow State Pedagogical University, 1/1, Malaya Pirogovskaya St, Moscow, 119991, Russian Federation
Rovshan Khalilov	Russian Institute for Advanced Study, Moscow State Pedagogical University, 1/1, Malaya Pirogovskaya St, Moscow, 119991, Russian Federation Department of Biophysics and Biochemistry, Baku State University, Baku, Azerbaijan Institute of Radiation Problems, Azerbaijan National Academy of Science, Baku, Azerbaijan
Soheila Montazersaheb	Molecular Medicine Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
Solmaz Maleki Dizaj	Dental and Periodontal Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
Soodabeh Davaran	Department of Medicinal Chemistry,School of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran
Vharoon Sharma Nunkoo	Faculty of Medicine and Pharmacy, Clinical Municipal Hospital, University of Oradea, Romania, Oradea
Yalda Jahanbani	Department of Medicinal Chemistry,School of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran

Yolanda Cruz Centro de Investigación en Ciencias de la Salud (CICSA), Facultad de Ciencias de la Salud Universidad Anáhuac México, Norte, Mexico

CHAPTER 1

Comorbidities Inducing Mild Cognitive Impairment, an Evaluation of the Risk Caused by some Pathological Conditions

Yolanda Cruz[1], Alejandra Romo[1], Roxana Rodríguez-Barrera[1], Almudena Chávez-Guerra[1], Macarena Fuentes[1] and **Antonio Ibarra[*, 1]**

[1] Centro de Investigación en Ciencias de la Salud (CICSA), Facultad de Ciencias de la Salud Universidad Anáhuac México Norte. Avenida Universidad Anáhuac 46, Lomas Anáhuac, Huixquilucan, Estado de Mexico, C.P. 52786

Abstract: Mild cognitive impairment has usually been associated with aging, however, in recent decades with the increase in the prevalence of pathologies such as obesity, diabetes mellitus, cardiovascular diseases, and even spinal cord injury, it has become evident that a significant percentage of people who suffer from one or more of these diseases are at greater risk of suffering from some level of cognitive impairment that can lead to the development of various types of dementia. In this chapter, we review the main characteristics and mechanisms that promote the development of this type of alteration in each of the mentioned pathologies and briefly describe the various ways in which they have been approached.

Keywords: Amnesic Memory, aging, Cognitive Domains, Diabetes Mellitus, Dysbiosis, Hypertension, Long-Term Potentiation, Low-Grade Inflammation, Mild Cognitive Impairment, Neurogenesis, Non-Amnestic Memory, Obesity, Stroke, Spinal Cord Injury.

INTRODUCTION

As life expectancy grows, so does the prevalence of neurodegenerative diseases. Mild cognitive impairment (MCI), with dementia as its most evident prognosis, has a profound impact on public health as well as on patient's life quality. Nowadays, 48 million people worldwide have been diagnosed with dementia, a number that is expected to rise to 131 million by 2050, yet clear diagnosis guidelines and standards of care for patients who suffer this debilitating disease are left wanting [1].

[*] **Corresponding author: Antonio Ibarra :**Centro de Investigación en Ciencias de la Salud (CICSA), Facultad de Ciencias de la Salud Universidad Anáhuac México Norte;Avenida Universidad Anáhuac 46, Lomas Anáhuac, Huixquilucan, Estado de Mexico ,C.P. 52786, México; Tel: (+55)-87-99610-8311; E-mail: jose.ibarra@anahuac.mx

Cognitive functions are neural processes that help us carry out a task; there are 6 main cognitive domains: learning and memory, social functioning, language, visuospatial function, complex attention and executive functioning [2].

Cognitive impairment refers to a deficit in at least one domain. The term MCI was first used to describe stage 3 of the global deterioration scale (GDS), in which the subject presents subtle deficits in cognition without meeting the criteria for dementia. In the Key Symposium at Sweden (2004), the definition expanded, it now includes the affectation not only in memory but in other cognitive domains, and MCI was sub-classified as: amnestic (aMCI), non-amnestic (naMCI), single and multi-domain. Amnestic subtype refers to the impairment in the ability to recall information; memory being affected. Non-amnestic refers to the impairment in at least one non-memory cognitive domain, whereas memory remains unaffected [2 - 4].

Amnestic MCI is associated with greater risk of developing dementia such as Alzheimer´s Disease (AD), whereas naMCI may progress to other syndromes such as frontotemporal dementia, primary progressive aphasia, dementia with Lewis bodies, among others. Multi-domain, as the name says so, refers to the impairment of multiple cognitive domains; therefore, patients manifest subtle problems in daily life activities. It might represent a more advanced stage of the neurodegenerative process [3, 5].

In 2011, the National Institute on Aging-Alzheimer´s Association included biochemical and neuroimaging biomarkers in the diagnostic criteria for MCI, as some of these biomarkers are seen in subjects with MCI, and may predict later conversion to AD. These risk factors include: apolipoprotein E (APOE) ε4 allele, lower β amyloid 1-42 (Aβ42), higher phosphorylated tau (P-tau), higher total tau (t-tau), amyloid PET, among others [4].

The prevalence of MCI is mainly reported in people older than 65 years old, and it is estimated to be between 3 to 22%, although currently it is underdiagnosed, as it is not usually recognized by primary care physicians; annually, 5 to 31% will progress to dementia [2, 6].

Cognitive impairment is diagnosed using the criteria established in the Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-V) [2]; it is diagnosed when there is a deterioration of one or more cognitive domains at a higher level than expected at given age and education level, confirmed in an objective manner by a professional, without impairing social nor work abilities [6]. Although, there are no specific tests to diagnose MCI as the differences between normal aging and MCI can be difficult to determine. Furthermore, cognitive impairment is different among patients, with some displaying a single

non-memory domain and others involving multiple cognitive domains. Once diagnosed, some people develop further neurodegenerative disorders such as dementia and AD, while others remain stable or even revert to pre-existing cognition levels [7].

The rising numbers of MCI have generated a surge of research from both clinical and investigation perspectives, but while a rising number of older adults suffer from different stages of pre-dementia, most remain undiagnosed [8]. Most doctors diagnose subjects with MCI based on evidence and symptoms provided by the patients themselves while trying to use reliable tools and techniques as to discriminate against those who present normal and pathological signs of aging. Criteria for MCI diagnosis was developed by a workgroup sponsored by the National Institute on Aging and the Alzheimer's Association, who agreed on the following common guidelines [9]:

1. A change in cognition recognized by the affected individual or observers
2. Existence of objective impairment in one or more cognitive domains: memory, planning, following instructions or decision-making processes being hindered
3. Independence in functional activities
4. Absence of dementia

Cognitive impairment is mostly associated to aging, but there are other diseases that can lead to its development, such as obesity, diabetes, cardiovascular diseases such as systemic arterial hypertension (SAH) and ischemia, spinal cord injury (SCI), among others. Each of these diseases has different mechanisms that lead to cognitive impairment, but they also share some of them. This chapter will discuss the mechanisms involved in the development of cognitive impairment in different diseases.

OBESITY AND COGNITIVE IMPAIRMENT

Definition and Epidemiology of Obesity

Obesity has become a social and psychological problem that affects around 650 million adults and 340 million children and adolescents worldwide [10]. It is characterized by being a chronic disease of multifactorial origin, which is defined as the excessive accumulation of adipose tissue in the body linked to a high risk of presenting other diseases. The World Health Organization (WHO) uses body mass index (BMI) as a metric to indicate body fatness, classifying obesity as a BMI $\geq$ 30 kg/m^2 [11].

CHAPTER 2

Tau-Targeted Therapy in Alzheimer's Disease - History and Current State

Anamaria Jurcau[1,*] and **Vharoon Sharma Nunkoo**[1]

[1] *University of Oradea, Faculty of Medicine and Pharmacy, Clinical Municipal Hospital, Dr. G. Curteanu", Oradea, Romania*

Abstract: The two main histopathological hallmarks still required for the diagnosis of Alzheimer's disease are the presence of amyloid plaques and intraneuronal neurofibrillary tangles formed mainly of tau protein. Normally, tau protein regulates intracellular trafficking and provides microtubule stability. However, in AD as well as in other tauopathies, there is a disruption in the normal function of tau, leading to the development of neurofibrillary tangles with disease-dependent ultrastructure of the tau filaments.

After several failures of trials with drugs trying to prevent the accumulation of amyloid, tau protein became another target of molecules designed to modify the course of AD.

Each stage in the development of tau pathology, from the expression of tau protein to its post-translational modifications, with the protein's aggregation and impaired clearance, presents opportunities for therapeutic intervention: reducing tau expression with antisense oligonucleotides, reducing tau phosphorylation with kinase inhibitors, inhibiting tau acetylation, tau deglycosylation, tau aggregation, modulating tau degradation, stabilizing the microtubules, as well as active or passive anti-tau immunotherapies (with various monoclonal antibodies), have been attempted or are still in trials, with rather inconclusive results so far. It appears that an efficient disease-modifying therapy is not yet available. Given the complex pathophysiology of Alzheimer's disease, most likely, a multi-targeted approach would be more effective.

Keywords: Alzheimer's disease, Anti-tau therapy, Microtubules, Mitochondrial dysfunction, Tauopathies, Tau protein.

[*] **Corresponding author Anamaria Jurcau:** The University of Oradea, Faculty of Medicine and Pharmacy, Oradea, Romania; E-mail:anamaria.jurcau@gmail.com

HISTORICAL BACKGROUND

Alois Alzheimer, a German physician and a pioneer of linking disease symptoms to microscopic brain changes, first met and examined Auguste D. in 1901 in Frankfurt. Although 1 year later he took a position in Munich, he was haunted by this case. Thus, in April 1906, when the patient died, he examined her brain and found impressive shrinkage and abnormal depositions in and around nerve cells. Today, more than 100 years after the presentation of Alzheimer's findings at the Conference held in Tübingen in November 1906 [1, 2], amyloid plaques and neurofibrillary tangles are still required for the pathological diagnosis of Alzheimer's disease [3].

Using the newly discovered electron microscopy technique, Terry and Kidd described the intraneuronal deposits in 1963 as being paired helical filaments [4, 5]. Further, in 1975, Weingarten and coworkers characterized these filaments as being a protein named tau, which is crucial for the assembly of tubulin into microtubules [6]. Interestingly, 1975 was the same year in which tau the lepton was also discovered by Perl *et al*. [7]. Soon thereafter, Cleveland and coworkers provided a biochemical characterization of tau [8, 9].

However, because monogenic mutations in the amyloid precursor protein (APP) or the presenilins involved in its processing can lead to phenotypes similar to AD, until recent years, research has focused mainly on these molecules. The discovery of tau mutations able to cause neurodegenerative diseases on their own [10] as well as of intracellular tau aggregates in several neurodegenerative diseases like progressive supranuclear palsy, frontotemporal lobar degeneration, corticobasal degeneration, or Pick's disease (collectively referred to as tauopathies) [11], boosted tau research and led to exploring several therapeutic strategies in neurodegenerative diseases [7, 12, 13].

NORMAL TAU PROTEIN STRUCTURE AND FUNCTION

The Tau Gene and Tau Isoforms

Human tau is encoded by the MAPT (microtubule-associated protein tau) gene located on chromosome 17q21 [14]. Alternative splicing generates mainly 6 isoforms of 37-46 kDa in the central nervous system (CNS), while a “big tau” isoform is found mainly in the peripheral nervous system [15, 16]. The six isoforms found in the CNS (Fig. **1**) differ by the presence of zero, one, or two N-terminal inserts and either 3 (3R) or 4 (4R) microtubule binding C-terminal inserts

[17]. Due to the developmentally regulated expression of tau, all 6 isoforms can be found in the adult human brain, while the fetal brain expresses only the shortest isoform (0N3R) [18].

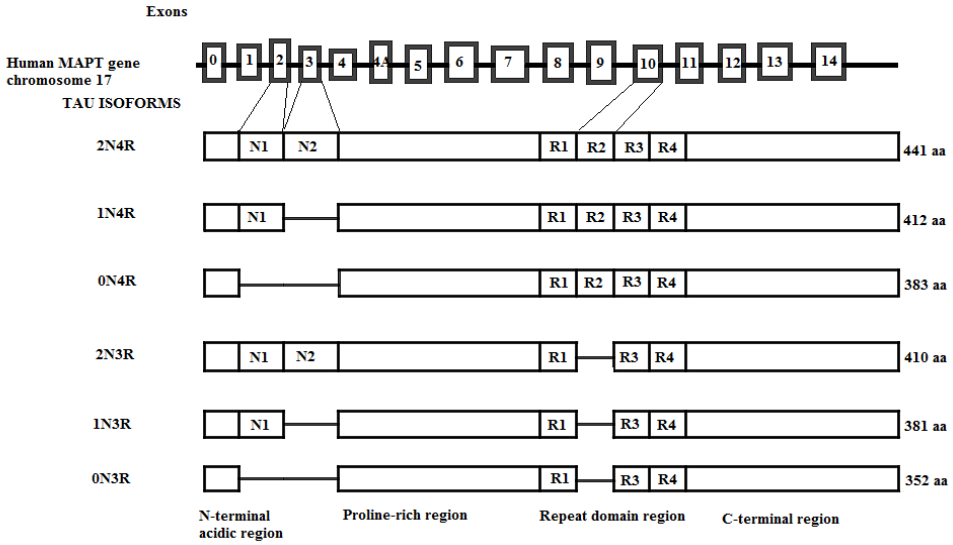

Fig. (1). Genomic structure of the human tau gene; of the 14 exons, exons 2, 3, and 10 are alternatively spliced, generating six tau isoforms in the adult brain. Exons 9, 11, and 12 each encode for a microtubule-binding repeat generating 3R tau isoforms. The presence of E10 adds an extra MT-binding repeat generating 4R tau isoforms. 3R and 4R tau isoforms further differ depending on the presence of exon 2 (1N) or exons 2 and 3 together (2N), while the absence of both exons generates 0N3R and 0N4R isoforms of tau. The number of aminoacids in each isoform is shown on the right.

Tau Protein Structure

The amino acid composition of tau is unusually hydrophilic [19], and the protein has an overall basic character. The charges have an asymmetrical distribution, with the amino-terminal being acidic and the carboxy-terminal being neutral. The middle region contains numerous prolines which harbor many epitopes of antibodies that are hyperphosphorylated in Alzheimer's disease [12].

Due to its hydrophilic character, the polypeptide chain of the protein is flexible and mobile. Tau is normally unfolded as opposed to most cytosolic proteins, which have a compact folded structure [20, 21]. To date, the “paperclip” conformation of tau is widely accepted, in which the C-terminus is folded over the microtubule-binding domain, and the N-terminus folds over the C-terminus [22], as shown in Fig. (**2**). This conformation is disrupted by tau phosphorylation [9].

CHAPTER 3

Implication of Dehydroepiandrosterone on Dementia Related to Oxidative Stress

Adriane Bello Klein[1], Alexandre Castro[1], Alex Sander da Rosa Araujo[1], Daiane da Rocha Janner[2] and **Maria Helena Vianna Metello Jacob[3,*]**

[1] *Federal University of Rio Grande do Sul (UFRGS), Institute of Basic Health Sciences, Physiology, R. Sarmento Leite, 500 – CEP 90035-190- Porto Alegre, RS,Brazil*

[2] *Federal University of Rio de Janeiro (UFRJ),Carlos Chagas Filho Institute of Biophysics – Neurogenesis Lab, Av. Carlos Chagas Filho, 373–CEP 21941-902, Rio de Janeiro, RJ,Brazil*

[3] *Montfort Hospital – Institut du Savoir, 745, Montreal Road, K1K 0T1 Ottawa, ON/Canada*

Abstract: The number of people living with dementia will increase worldwide over the coming decades as the population ages. The aging of the brain is associated with oxidative stress. Evidence of increased oxidative stress has been seen in Alzheimer's disease (the most common cause of dementia), contributing to the formation of amyloid plaques and neurofibrillary tangles. Dehydroepiandrosterone is a physiologically active steroid hormone that declines with aging and is associated with aging-related neurodegeneration. Exogenous dehydroepiandrosterone can exert an antioxidant or prooxidant effect, depending on the dose and tissue specificity. Dehydroepiandrosterone biosynthesis in the brains of rats, bovines, and humans can be mediated by prooxidant agents, such as Fe^{2+} and β-amyloid peptides. A-β can provoke an increase in oxygen free radicals in cells, and this rise in reactive oxygen species modulates dehydroepiandrosterone levels. Also, studies have demonstrated that dehydroepiandrosterone treatment may modulate Akt (a serine/threonine kinase implicated in neuronal survival), and its activation could be changed with aging. Despite the numerous studies, the mechanism of action of dehydroepiandrosterone and its relationship with dementia or improvement in behaviours associated with memory and motor activity should still be elucidated as relates to dosage, temporal treatment window, besides its acute and chronic effects. A better understanding of the physiological role of dehydroepiandrosterone in the aging process may be of benefit to the development of novel strategies in the treatment of dementia.

[*] **Corresponding author Maria Helena vianna Metello Jacob :** Montfort Hospital – Institut du Savoir, 745, Montreal Road, K1K 0T1 Ottawa, ON,Canada; Tel: (+1) 613-746-4621; E-mail: mhvmjacob@hotmail.com

[#] There is no first author, and all authors contributed similarly.

Dr. José Juan Antonio Ibarra Arias (Eds.)

Keywords: Aging, Akt, Dementia, Dehydroepiandrosterone, Dehydroepiandrosterone Sulphate, Oxidative Stress, Neuroprotection, Neuro- steroids, Reactive Oxygen Species, Steroids.

INTRODUCTION

The number of people living with dementia will increase worldwide over the coming decades as the population ages. Current estimates suggest that the number of adults living with dementia will increase slightly less than twofold in Europe, somewhat more than twofold in North America, threefold in Asia, and fourfold in Latin America and Africa from 2015 to 2050 [1]. Dementia is a global pandemic, and the majority of people living with dementia live in low- and middle-income countries where access to health services, support, care, and social protection is extremely limited.

A low level of education is a well-known risk factor for dementia, which is generally associated with low socioeconomic status and reduced access to health care, from the prenatal period to older ages. Therefore, a low level of education could increase the risk of dementia by limiting the adequate diagnosis and treatment of co-morbidities, especially diabetes mellitus and cardiovascular disease, as well as being often associated with insufficient nutritional status [2]. These associated factors may explain the rise in numbers; while 37% of people living with dementia live in high-income countries, 63% live in low-and-middle-income countries [1].

Aging, an inevitable and natural process, is related to increased oxidative stress (OS) and chronic inflammation [3, 4]. Similarly, aging of the brain is associated with OS and cumulative inflammation, which explains why older people predispose to developing neurodegenerative pathologies. Inflammation is a normal physiological process that is essential to maintain homeostasis. Under normal conditions, the inflammation-repair cycle works efficiently during youthful years, and then it is affected by aging, producing a relatively impaired ability to regenerate damaged tissues and thus contributing to a more pro-inflammatory phenotype [4]. Age-related neuroinflammation appears to be associated with the fact that microglia faces important functional and immunophenotypic changes with aging, being exposed to augmented pro-inflammatory responses [5]. In fact, aging can be defined as a loss of homeostasis due to chronic OS affecting especially the regulatory systems (endocrine, immune, and nervous systems) [6].

The presence of enhanced reactive oxygen species (ROS) in neurons leads to OS in the central nervous system (CNS), presenting a big threat to its integrity which can induce neurodegenerative disorders [7]. Dehydroepiandrosterone (DHEA),

which is a physiologically active steroid hormone, declines with aging and is associated with aging-related neurodegeneration. Also seen as a neurosteroid, DHEA has also been found to protect rat and human hippocampal neuronal cells against OS-induced cellular damage [8]. Given the neuroprotective and cognitive-enhancing properties of DHEA, this neuroactive steroid [9, 10] may be of particular importance in the treatment of neurodegeneration diseases, including dementia. DHEA presents a dual effect linked to OS. Exogenous DHEA can exert an antioxidant [11 - 14] or prooxidant [15 - 18] effect depending on the dose and tissue specificity.

Much remains inconclusive about DHEA's mode of action in the human body or the rationale for its age-related decline. Given the commonly accepted phenomenon of accelerated aging in many chronic diseases, knowledge about the possible role of DHEA as a therapeutic or preventative benefit should be investigated. A better understanding of the physiological role of DHEA in the aging process in CNS may be of benefit to the development of novel strategies in the treatment of dementia. It is important to note that DHEA has been used as an anti-aging supplement, but there is a lack of information based on randomized controlled trials studies on DHEA supplementation and health outcomes. Although mechanisms of action have been pointed out in experimental models, further large clinical trials are necessary to better identify the clinical role of DHEA and to elucidate benefits *versus* potential risks. In this chapter, we contribute to a more comprehensive scenario of what is known about three important elements strongly implicated in dementia: aging, OS, and DHEA.

The Implication of Aging and Oxidative Stress in Dementia

Defining aging, as well as understanding by what mechanisms we age, is still a complicated task to gerontological science. There is a broad discussion of whether aging is a physiological process or a random set of damage events that result in the impairment of life conditions, disease development, and organismal system failure [19]. Moreover, the use of both aging and senescence terms as synonymous is also controversial; and even though senescence can exert a relevant role in the progression of aging, it also seems to be involved with beneficial effects, such as neoplasm control, cellular plasticity, and stress response [19].

In the biological spectrum, on the other hand, aging can represent all cellular alterations (adverse or not) that may happen during the whole life process [20]. Factors associated with aging progression can be represented by reduced telomere maintenance, genetic and epigenetic alterations, immunological decline, and mitochondrial dysfunction. In this sense, the reduction of homeostasis control

CHAPTER 4

Emerging Nanotherapeutic Strategies in Alzheimer's Disease

Soheila Montazersaheb[1], Elham Ahmadian[2], Solmaz Maleki Dizaj[3], Yalda Jahanbani[4], Soodabeh Davaran[4], Irada Huseynova[5], Cumali Keskin[6], Renad I. Zhdanov[7,8], Rovshan Khalilov[7,9,10] and **Aziz Eftekhari[7,11,*]**

[1] *Molecular Medicine Research Center, Tabriz University of Medical Sciences, Tabriz, Iran*

[2] *Kidney Research Center, Tabriz University of Medical Sciences, Tabriz, Iran*

[3] *Dental and Periodontal Research Center, Tabriz University of Medical Sciences, Tabriz, Iran*

[4] *Department of Medicinal Chemistry, School of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran*

[5] *Institute of Molecular Biology & Biotechnologies, Azerbaijan National Academy of Sciences, 11 Izzat Nabiyev, Baku AZ 1073, Azerbaijan*

[6] *Medical Laboratory Techniques, Vocational Higher School of Healthcare Studies, Mardin Artuklu University, Mardin, Turkey*

[7] *Russian Institute for Advanced Study, Moscow State Pedagogical University, 1/1, Malaya Pirogovskaya St, Moscow, 119991, Russian Federation*

[8] *Kazan Federal University, 420008, Kremlevskaya 18, Kazan, Russia*

[9] *Department of Biophysics and Biochemistry, Baku State University, Baku, Azerbaijan*

[10] *Institute of Radiation Problems, Azerbaijan National Academy of Science, Baku, Azerbaijan*

[11] *Pharmacology and Toxicology Department, Maragheh University of Medical Sciences, Maragheh, Iran*

Abstract: Recent nanotechnological advancements have opened new windows of hope for the treatment of neurodegenerative diseases and all of these new methods are rapidly evolving. Alzheimer's disease (AD) treatment based on neuroprotective and neurogenerative techniques has been advancing rapidly in recent decades, and the use of nanotechnology developments such as polymers, emulsions, lipo-carriers, solid lipid carriers, carbon nanotubes, and metal-based carriers has been very effective in both diagnosis and treatment methods. Targeted drug delivery is one of the most important concerns in the AD treatment approaches because the 'blood-brain barrier' or the 'blood-cerebrospinal fluid barrier is a serious obstacle for delivering a therapeutic agent to the desired location, but the use of nanocarriers have provided acceptable results in this area. It seems that the use of nanotechnology in approving a successful treatment

[*] **Corresponding author Aziz Eftekhari:** Maragheh University of Medical Sciences, Maragheh, Iran; Tel: +989364655619; E-mail:ftekhari@ymail.com

Dr. José Juan Antonio Ibarra Arias (Eds.)

method for Alzheimer's is inevitable and this review has collected a complete copy of the recent nanotechnology-based approaches for the treatment of AD.

Keywords: Alzheimer's Disease, Amyloid β-protein, Dementia, Drug Delivery, Magnetic Nanoparticles, Nanomedicine, Nanotechnology, Neurodegenerative Diseases, Polymeric Nanoparticles, Targeted Drug Delivery.

INTRODUCTION

Alzheimer's disease (AD) is a progressive degenerative disease of the central nervous system in the elderly population, accounting for an estimated 60–80% of dementia cases worldwide. This devastating disease is characterized by the irreversible loss of neurons and synapses in the brain, resulting in cognitive and intellectual deficits as well as alterations in behavioral traits such as anhedonia- and anxiety-like symptoms [1]. The progressive and brain decay is attributed to the formation of senile plaques and neurofibrillary tangles (NFTs) in the hippocampus, which are the most prominent pathological hallmarks of AD. Extracellular senile plaques are formed by amyloid-β42 peptide (Aβ42) and intracellular NFTs composed of hyperphosphorylated TAU protein [2]. It is also important to note that the formation of these plaques can start approximately 20 years before appearance of the clinical symptoms in patients with AD [3]. The histopathologic features of AD are strongly associated with hippocampal neuronal degeneration, synaptic dysfunction and loss, and aneuploidy. In addition, neuronal inflammation, mitochondrial dysfunction, and impaired lymphatic system have a major role in the course of AD. The pathological mechanisms in AD can enhance the production of ROS, resulting in oxidative stress-mediated signaling cascades. In this context, increasing cell stress, microglial dysfunctions, and upregulation of inflammatory cytokines lead to neuronal cell death in AD. Apart from these, various physiological parameters and lifestyle factors are also involved in the onset of AD [4, 5]. Collectively, the complex pathophysiology of AD results in cholinergic neurotransmission deficits in the brain of patients with AD. With this background, there is an urgent need to deal with this chronic disease. Multiple efforts have been made to slow the degenerative process; however, little success has been achieved [6]. In general, two types of treatments are available for patients with AD; symptomatic treatments and targeting approaches [7]. Nanotechnology-based medicine is a novel therapeutic approach that offers opportunities for prevention, diagnosis, and AD therapy. Promising anti-AD strategies are based on targeting the cholinergic system, Aβ protein, and other AD-related factors [8].

In general, AD is diagnosed with memory, cognition, and behavioral impairment (dementia), all of these complications occur as a result of progressive neurodegeneration. AD in the final stages may eventually lead to mood fluctuations and fatal delirium [1]. Due to the progress of different communities towards aging, AD has become a global concern. According to the statistics provided, nearly 36 million inhabitants have been reported with dementia-AD since 2010; the number of reported clinical cases is expected to reach 65.7 million by 2030 [9]. Numerous clinical data suggested that during AD, severe impairment in cholinergic–neurotransmitter systems occurs; it seems the cause of this defect is suppression of acetylcholine (responsible for neural synapse) by Acetyl-cholinesterase (AChE) activity [10]. In addition to the AChE activity, the activation of the glutamatergic system also plays an important role in AD pathology [11]. Based on two processes mentioned that occur during AD, few drug candidates such as tacrine, donepezil, rivastigmine, galantamine (AChE inhibitors), and memantine (NMDA inhibitor) were developed by researchers [12, 13]. Despite all the investments of pharmaceutical bodies such as Merck & Co., Lily, Pfizer, *etc*. and the efforts of researchers, these drugs in terms of pharmacokinetic (half-life) profiles of the drugs in the biological system and existence of side effects did not provide the desired results [14, 15]. These drugs have shown successful results in pre-clinical studies but their efficacy in human trials was not satisfactory; of course, patient withdrawal in clinical trials and not retention to a full study term, has been a big problem to access comprehensive information [16]. But in addition to these, therapeutic failures can be caused by factors such as poor pharmacokinetics or low bioavailability, chemical nature (absorption in biological – blood brain barrier system), volatility (oxidation, hydrolysis) of the drugs in question [16 - 18].

Biodistribution, targeting and BBB permeability are the main challenges for drug delivery into AD. One of the main important areas to solve these challenges is the use of nanotechnology approaches in drug delivery systems to achieve improved bioavailability and kinetic profile of different types of drugs in biological systems [19]. Functionalized NPs resulted in a greater biodistribution of the formulation in the brain than the intravenous administration of the NPS [20]. Nanotechnology made possible targeting and safe delivery of drugs to different parts of the body [21]. The controlled release profile of drugs improves with using of sustained release of nano-drug delivery systems [22]. Accordingly, the nanotechnology-based delivery systems can influence the BBB permeability *via* tethering AD drugs onto the surfaces of the nanoparticles [23]. It is important that the use of nanotechnology approaches in drug delivery systems improved the bioavailability and kinetic profile of different types of drugs in biological systems significantly [19 , 22].

CHAPTER 5

Polyphenol Compounds as Potential Therapeutic Agents in Alzheimer's Disease

Érika Paiva de Moura[1], Alex France Messias Monteiro[1], Natan Dias Fernandes[1], Herbert Igor Rodrigues de Medeiros[1], Igor José dos Santos Nascimentos[2], Marcus Tullius Scotti[1], Francisco Jaime Bezerra Mendonça Júnior[3], Edeildo Ferreira da Silva-Júnior[*, 2] and **Luciana Scotti[1,4]**

[1] Postgraduate Program in Natural and Bioactive Synthetic Products, Health Sciences Center, Federal University of Paraíba, Castelo Branco Street, João Pessoa, PB , Brazil

[2] Chemistry and Biotechnology Institute, Federal University of Alagoas, 57072-970, Maceió, AL , Brazil

[3] Laboratory of Synthesis and Drug Delivery, State University of Paraíba, Horácio Trajano de Oliveira Street, João Pessoa, PB , Brazil

[4] Teaching and Research Management - University Hospital of the Federal University of Paraíba, João Pessoa, PB , Brazil

Abstract: According to the World Health Organization (WHO), dementia is a syndrome that affects thoughts, memory, the ability to perform day-to-day activities, and behavior. Alzheimer's disease (AD) corresponds to almost 70% of dementia cases, affecting mainly the elderly over 60 years old, causing physical, psychological, social, and economic impacts. Whether of natural or synthetic origin, the polyphenols and their derivatives have great versatility in terms of biological activity, as can be seen in the literature, exhibiting different properties, such as anti-inflammatory, anti-tumor, anti-viral, anti-microbial, and others. Among therapeutic alternatives are polyphenols and their derivatives as a molecular class broadly studied against neurodegenerative diseases, including AD. This chapter consists of a literary review of some polyphenols and derivatives with proven activity against AD, thus showing their importance among the other molecular classes, when it comes to proposing new bioactive agents against AD. Many targets are studied for this disease, since the pathogenesis of AD requires clarification and approved drugs only delay the evolution of the disease, such as donepezil hydrochloride, galantamine, among others. In addition to encouraging new studies by relating polyphenols and derivatives targeting AD, this work can assist research groups by providing some recent studies that have proven this relationship. At the end of this research, it is possible to realize the importance and applicability of these compounds in AD.

[*] **Corresponding author Edeildo Ferreira da Silva-Júnior:** Laboratory of Medicinal Chemistry - LMC, Chemistry and Biotechnology Institute, Federal University of Alagoas, Brazil; Tel: (+55)-87-99610-8311; Email: edeildo.junior@esenfar.ufal.br

Dr. José Juan Antonio Ibarra Arias (Eds.)

Keywords: Alzheimer's Disease, Amyloid-Beta, Aβ Amyloid Fibrils, BACE, Polyphenols .

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disorder that is becoming more common with the aging of the world's population, where it is estimated that one in every 85 people will have AD, in 2050 [1]. The disease is characterized by the progressive deterioration of cognitive functions due to brain atrophy, resulting from the death of neurons and degeneration of synapses in the hippocampus [2]. Thus, individuals with AD may experience memory loss, difficulty completing daily tasks, confusion with time or place, and learning problems [3].

Apart from the reduction in the brain volume, AD has other hallmarks, such as extracellular plaques containing amyloid-beta (Aβ) and intracellular neurofibrillary tangles containing hyperphosphorylated Tau protein [4]. Aβ is formed through the cleavage of amyloid precursor protein (APP) by three endoproteases, being α-secretase, β-secretase (BACE), and γ-secretase. These are responsible for cutting APP in different positions and thus producing Aβ peptides, ranging in length (23, 40, 42, or 56 amino acids) [5, 6]. As α-secretase cleavage does not produce complete Aβ, this protease does not participate in the development of AD, whereas BACE and γ-secretase are associated with the disease by producing various Aβ isoforms which can aggregate and form senile plaques [7]. In normal individuals, Aβ peptides removed from APP by actions of BACE and γ-secretase are released into the extracellular medium and rapidly degraded, while in elderly individuals the metabolic ability to degrade Aβ is decreased and Aβ peptides may be accumulated, inducing the formation of Aβ amyloid fibrils (fAβ) that can originate senile plaques and, consequently, cause neurotoxicity and induction of the Tau pathology [8].

Phosphorylation associated with Tau protein pathology has been the focus of recent researches, in which the most studied Tau kinases are proline-directed kinases, such as glycogen synthase kinase-3β (GSK-3β), mitogen-activated protein kinase (MAPK), among others [9]. However, the main Tau kinase is the active GSK-3β which, when increased in AD patients' brains, triggers irregular patterns of the Tau phosphorylation, which contributes to the disease progression [10]. One of the biological functions of Tau consists of its connection to the microtubule and thus regulating axonal transports. However, Tau phosphorylation can lead to its aggregation and as a consequence, it decreases the levels of soluble functional Tau and hinders the axonal transport, promoting neurodegeneration [11].

Recently, extensive studies suggest that soluble forms of A β produced during fibrillization, known as A β oligomers (A β O), are toxic species in AD capable of triggering a harmful cascade, damaging neurons and synapses [12]. A β O can cause toxicity by directly interacting with membranes and receptors and can be organized in different structures, such as dimers, trimers, tetramers, pentamers, decamers, dodecamers, among other forms [13]. Although pathological hallmarks of AD are considered to be the increase in the amount of A β monomers and the development of amyloid plaques, more research reports which A β O is a type of A β most strongly associated the severity of dementia in humans [14].

AD is also related to decreased brain levels of the neurotransmitter acetylcholine (ACh), where there is a failure in cholinergic neurotransmission that affects the brain's cognitive processes [15]. Thus, the recovery of ACh levels may be determinant for the treatment of AD, in which the regulation of these levels occurs by two different enzymes, being acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) [16]. AChE is found at high concentrations in the brain, while BuChE is distributed throughout the body, acting as cholinesterases (ChEs) extremely efficient since they cleave more than 10,000 ACh molecules *per* second [17]. In the brain of a healthy individual, AChE predominates over BuChE, but during the development of AD, AChE activity declines while BuChE activity increases [18].

The literature reports that several therapeutic targets have been investigated for the treatment of AD, such as proteins (Aβ and Tau), enzymes (BACE, γ-secretase, ChEs, and GSK-3β), receptors (cholinergic, dopaminergic, glutamatergic, among others), and processes/pathway (oxidative stress, neurogenesis, excitotoxicity, among others) involved in the pathogenesis of AD [19, 20]. The complicated pathogenesis of AD leads to the failure of several promising drug candidates in clinical trials, making it difficult to develop new drugs [21]. Currently, approved anti-AD drugs are related to memory recovery, where the AChE inhibition improves the cholinergic defect [22]. Thus, the current drug therapy for AD only attenuates the symptoms and does not interfere in the mechanisms related to disease progression. In this context, the search for efficient therapeutic approaches is an unmet need [23, 24].

Polyphenols are a class of natural, synthetic, or semi-synthetic organic compounds that are characterized by the presence of one or more aromatic rings with one or more hydroxyl groups [25]. According to their chemical structures, they can be classified into flavonoids, such as isoflavones, flavonols, flavones, neoflavonoids, chalcones, and others; also, nonflavonoids, such as stilbenoids, phenolic acids, and phenolic amides are polyphenols [26]. Polyphenols can be

SUBJECT INDEX

A

B

C

D

E

F

G

H

I

K

L

M

N

O

P

U

V