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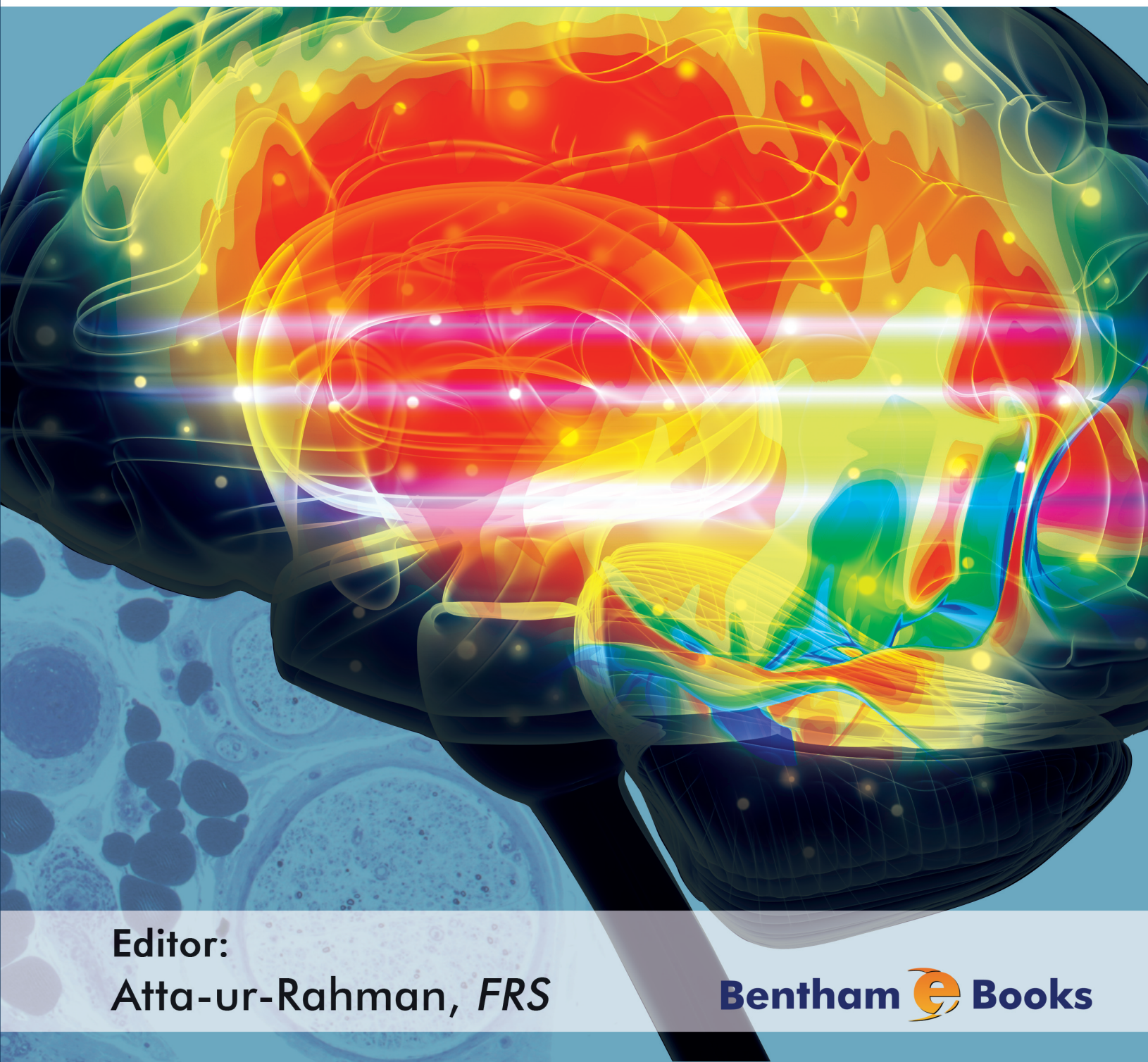

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Frontiers in Clinical Drug Research - Alzheimer Disorders

(Volume 6)

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PREFACE

The book series, "*Frontiers in Clinical Drug Research – Alzheimer Disorders*", is intended to present the important advancements in the field in the form of cutting edge reviews written by experts. *Volume 6* of this eBook series is a compilation of seven well written chapters contributed by prominent researchers in the field. It includes the treatment of brain inflammation, stem cell strategies, retinal neurodegeneration, pathophysiology of Alzheimer disease, and a number of other related areas.

Chapter 1 by Adams discusses the use of plant medicines as an alternative treatment to decrease the progression of Alzheimer's disease (AD). In chapter 2, Haigang Gu describes the recent progress of stem cell strategies for AD modeling and therapy. Cordeiro *et al*. in chapter 3 focus on the retinal neurodegeneration in AD. The pathological similarities between AD and eye diseases are also discussed. In Chapter 4, Gupta & Jhawat highlight the pathophysiology of Alzheimer disease with respect to the current drug therapy.

In chapter 5, Abdelhamid and Wu present the use of biological mass spectrometry for the diagnosis of Alzheimer's disease. This review also highlights the recent developments in disease diagnosis using mass spectrometry. Chapter 6 by Herrera emphasizes the structure-activity relationship of melanin as a source of energy. The last chapter by Suzuki *et al*., discusses the neuro-protective properties of the fungus *Isaria japonica* (IJ). The results showed that products derived from IJ may prevent or decrease the impact of dementia, especially AD.

The 6th 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

The Treatment of Brain Inflammation in Alzheimer's Disease. Can Traditional Medicines Help?

James David Adams*

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Abstract: The blood brain barrier degenerates in many people as they age. This degeneration can lead to inflammation, amyloid accumulation, neuron loss, tangle accumulation and dementia. Damage to the blood brain barrier may involve oxygen radical production through a visfatin mediated mechanism. Several plant medicines have been traditionally used to decrease the progression of Alzheimer's disease. Antioxidant mechanisms of action have been described for these medicines that may protect the blood brain barrier. These plant medicines provide alternative treatments for Alzheimer's disease.

Keywords: Alzheimer's disease, Anti-inflammatory prevention, Plant medicines.

INTRODUCTION

Alzheimer's disease (AD) involves neurodegeneration induced by amyloidβ. This neurodegeneration results in loss of neurons, plaque and tangle formation and ultimately in dementia. Many AD patients are treated with acetylcholinesterase inhibitors to slow the progression of mild AD. Eventually, most AD patients die from pneumonia and not neurodegeneration.

The current consensus is that AD is caused by amyloidβ toxicity in the brain [1]. It is clear that extracellular amyloidβ is toxic to neurons. Amyloidβ aggregates into fibrils, sheets and plaques. Some intermediate amyloid protein aggregates in the plaque formation process are toxic to neurons.

The role of inflammation in the pathophysiology of AD is well established [1]. Inflammation in AD can be secondary to amyloidβ accumulation. In other words, amyloidβ causes inflammation in the brain. Inflammation can also occur early in

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Atta-ur-Rahman (Ed.)

the disease process and initiate amyloidβ accumulation and AD pathology [2]. This inflammation involves microglial cells, astrocytes, perivascular macrophages and monocytes that infiltrate into the brain [2]. There are a number of different inflammatory molecules that are produced in the brain in this inflammatory process and as a consequence of amyloidβ production including chemokines, complement molecules, cytokines, inflammatory and acute phase proteins, cyclooxygenase-2, and free radicals [2 - 5].

Tau phosphorylation leading to tangle formation may occur as the result of amyloidβ oligomer toxicity [1]. Microglial and astrocytic activation are also involved in alteration of tau phosphorylation [1]. Neurofibrillary tangles are frequently found in AD brains.

The question that remains unanswered is why does amyloidβ production increase in the brains of people who will develop AD? This question can be avoided by claiming that 100% of people will develop AD if they live long enough. In other words, amyloidβ accumulation is a natural process in the brain that cannot be avoided. However, many very old people do not develop AD.

Anti-inflammatory Agents in AD

Several epidemiological studies have examined the use of anti-inflammatory drugs in patients and have found that the use of these drugs may decrease the induction of AD. These studies have been critically reviewed [2, 5, 6]. The use of indomethacin was reported to slow the progression of AD [7]. This finding was later disputed [8]. Patients suffering from arthritis have a decreased risk of developing AD, perhaps because of their use of anti-inflammatory agents [9]. Several other reports have failed to show a protective effect of anti-inflammatory agents in the progression or development of AD. In addition, several attempts to slow the progression of AD with various anti-inflammatory drugs have failed to show an effect. It must be remembered that oral nonsteroidal anti-inflammatory agents (NSAIDs) are very toxic, especially to the elderly. NSAIDs have effects on prostaglandins, lipoxins, resolvins, thromboxanes and other lipid metabolites. NSAIDs cause strokes, heart attacks, kidney damage and ulcers. They cause 42,000 or more deaths in the US every year. NSAIDs should be avoided in trials that hope to delay the progression of AD. Steroids damage the hippocampus and should also be avoided [10]. Perhaps the choice of anti-inflammatory agent has been inappropriate so far. In addition, the doses chosen may have been inappropriate in past studies. The doses chosen were probably too high and induced too much toxicity.

Risk Factors for Developing AD

If all people get AD with age, then the only risk factor for developing AD should be age. However, there are other risk factors that increase the chance of developing AD. The risk factors for developing AD are age, head trauma, high blood pressure, high blood cholesterol, diabetes, cardiovascular disease, atrial fibrillation, apolipoprotein E4, thrombosis, peripheral inflammatory factors, decreased muscle mass and high alcohol consumption [11 - 13]. Women are more likely to develop AD than men [11 - 13]. Brain trauma can cause gliosis, inflammation and deleterious changes to the brain that may be important in AD. Peripheral inflammatory factors cause high blood pressure, high blood cholesterol, type 2 diabetes, cardiovascular disease, atrial fibrillation and thrombosis [14]. These peripheral inflammatory factors include adipokines made in visceral and ectopic fat that are released into the blood. Inflammatory adipokines include visfatin, leptin, resistin, tumor necrosis factor α, IL-6 and others.

As people age, visceral and ectopic fat deposits develop. Toxic lifestyles, including lack of exercise and over eating, cause fat accumulation. Ectopic fat is fat that surrounds arteries, infiltrates muscles and other sites. Visceral fat accumulates in the peritoneal cavity. Therefore risk factors for AD are probably high blood levels of inflammatory adipokines released by visceral and ectopic fat. Obesity has increased greatly since the 1980s as reported by the Centers for Disease Control (www.cdc.gov). The incidence of AD has also increased greatly since 1980, in parallel with the increase in visceral obesity [15]. According to the Centers for Disease Control, among the entire US population, 93,500 people died while affected with AD in 2014. The entire US population, age adjusted death rate from AD increased by 39% from 2000 through 2010.

Several studies found the incidence of AD decreased over the last 25 years or more by about 25% [16 - 19], in spite of the increases in obesity and type 2 diabetes. These studies were done in selected populations and point to better education and better treatment of heart disease as ways to prevent AD. This indicates that patients who are educated enough about risk factors for AD to seek out better health care and other healthy lifestyle practices have a decreased risk. Weight reduction can be part of a healthy lifestyle. All of these studies advise that patients who practice healthy lifestyles have a decreased risk of developing AD. Is the incidence of AD actually decreasing in the US? The answer is clearly that the incidence of AD is increasing in the total US population.

Apolipoprotein E4 transports lipids inside the brain, including cholesterol and triglycerides. When triglycerides accumulate, the alternative fat ceramide is made

CHAPTER 2

Stem Cell Strategies for the Modeling and Therapy of Alzheimer's Disease

Haigang Gu*

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Abstract: Alzheimer's disease (AD) is the most common form of dementia in aged populations.AD is characterized by a progressive decline in memory and cognitive function, accompanied with behavioral changes such as confusion, irritability and aggression, mood swings, language breakdown and eventually long-term memory loss. The most significantly pathological findings in the brains affected by AD are senile plaques (SP), neurofibrillary tangles (NFT) and neuronal loss or degeneration, particularly in the areas connected to the cerebral cortex and hippocampus.The most prominence among these regions is the basal forebrain cholinergic neurons. Many AD studies and clinical trials focus on inhibiting the formation of extracellular senile plaques and intracellular neurofibrillary tangles to prevent or halt disease progression. For example, the Food and Drug Association (FDA) has approved three acetyl-cholinesterase inhibitors (AChEIs), donepezil, rivastigmine and galantamine as AD therapy. Elevating the neurotransmitter acetylcholine by AChEIs has been shown to benefit cognitive functions in patients. Excitotoxicity caused by glutamatergic synaptic dysfunction contributes to cognitive AD symptoms. Another FDA-approved AD drug, the N-methyl-D-aspartate (NMDA) receptor antagonist memantine, is thought to alleviate the excitotoxicity. To date, however, none of these treatments have been shown to be safe and effective in clinic. Stem cell therapy is a promising therapeutic strategy, which has been shown to replace the neurodegenerative cholinergic neurons and provide exogenous neurotrophic factors in AD brains. Stem cells have been used as therapy of neurodegenerative diseases to deliver RNAi to the brains and regulate the expression of neprilysin, an amyloid-β (Aβ)-degrading enzyme. More recently, stem cells, especially induced pluripotent stem cells (IPSCs), have been used for AD modeling and drug screening. However, effective drugs or other interventions that stop or delay progression of AD remain elusive. Due to the multifaceted features of AD, further investigations of AD therapies are necessary. This review will discuss the recent progress of stem cell strategies for AD modeling and therapy.

Keywords: Alzheimer's disease, Drug discovery, Small molecules, Stem cells, Therapy.

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Atta-ur-Rahman (Ed.)

1. INTRODUCTION

The most common type of dementia in aged populations is Alzheimer's disease (AD), which is characterized by a progressive decline in memory and cognitive function. Alzheimer's disease is accompanied with behavioral changes such as confusion, irritability and aggression, mood swings and language breakdown. In the late stage of AD, patients lose the functions of movement, learning and memory [1, 2]. The cause of initiation and progression of AD are not well understood. Previous investigations have shown that the incidence of AD is strongly associated with aging. The most significantly pathological findings in brains affected by AD are senile plaques (SP), neurofibrillary tangles (NFT), neuronal loss or degeneration, particularly in the areas connected to the cerebral cortex and hippocampus.The most prominent among the regions is the basal forebrain (BF) cholinergic neurons [3 - 7]. Cholinergic neurons of BF express both the low affinity neurotrophin receptor (P^{75NTF}) and tropomyosin receptor kinase A (TrkA), and respond to neurotrophic factors (NTFs) by increased activity of choline acetyltransferase (ChAT). Neurotrophic factors are also important in the development of neurons and maintaining normal functions of the nervous system, such as outgrowth of axons and neuritis, pathfinding, synaptic genesis and neural circuit formation. Neurotrophic factors have been extensively used for therapeutic studies in the experimental models of AD [8, 9]. Moreover, NTFs have shown beneficial effects in other neurodegenerative diseases, such Parkinson’s disease (PD), Huntington's disease (HD), spinal cord injury (SCI) and stroke. However, NTFs are macromolecular proteins that do not readily cross the blood-brain barrier (BBB). Efficient delivery of NTFs into the central nervous system remains challenging.

Strategies to decrease the degradation of acetylcholine in the central nervous system usually involve increasing cholinergic function and improving cognitive functions in AD patients. Some small molecules have been developed to inhibit the cleavage of acetylcholine. To date, cholinesterase inhibitors, such as donepezil, galantamine and rivastigmine, are available for the treatment of AD [10, 11], but their effects must be further investigated. Many patients do not show functional benefit after cholinesterase inhibitor therapy. Furthermore, medication application does not stop the progression of AD. Although grafting embryonic cholinergic neurons has been shown to increase cholinergic function in animal models of AD, this strategy is not clinically feasible due to the limited availability of fetal tissue and ethical concerns. Due to the self-renewal ability of stem cells, sufficient numbers of neurons can be generated for both research and transplantation therapy within a short period of time. Moreover, stem cells have the potential to differentiate into different types of somatic cells. For example, neural stem cells (NSCs) have been successfully cultured, which solves the

problem of using human fetal donors. Neural stem cells can generate neurons, astrocytes and oligodendroglia in response to environmental signals, including NTFs, retinoic acid (RA) and growth factors. Stem cell-derived neurons can migrate and integrate with host neurons in the brain and spinal cord. Furthermore, stem cell-derived glial cells can secret NTFs to promote the survival of degenerative neurons [12 - 15]. Induced pluripotent stem cells (IPSCs) allow the development of personalized medicine. For example, a specific patient's IPSCs could be induced to differentiate into cholinergic neurons. And then, the best drug candidates for this patient can be identified using screening a drug library against their IPSC-derived cholinergic neurons [3, 4].

Although many basic scientific and clinical studies have shown that drug treatment could improve cognitive function and memory of AD patients, delaying and/or stopping neuron loss and degeneration is still a considerable challenge [2, 16]. Due to the multifaceted features of AD, more works remain to be done to explore the novel specific therapeutics (Fig. **1**). Combining different therapies must be considered in the future. This review discusses the recent progress in the field of AD, focusing on stem cell therapeutic strategies.

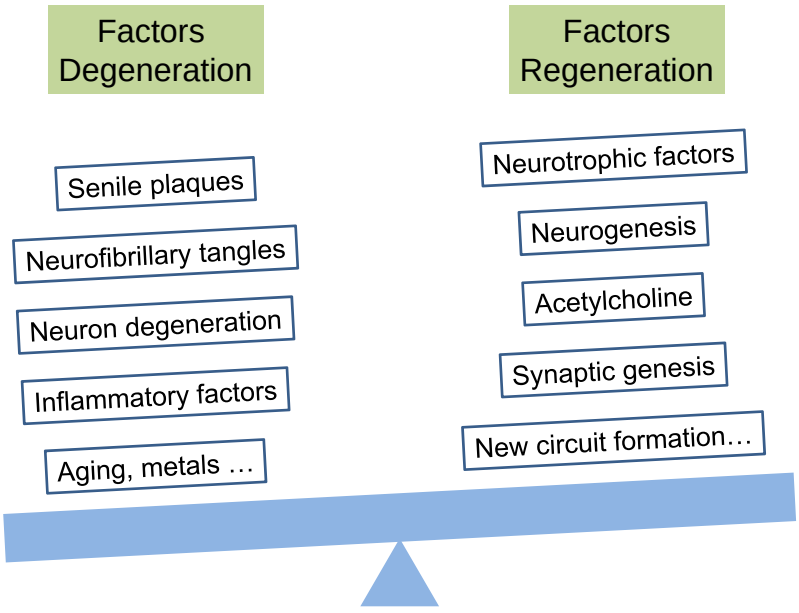

Fig. (1). Factors affect Alzheimer's disease (AD). Loss of the balance between degeneration and regeneration causes AD.

CHAPTER 3

Retinal Neurodegeneration in Alzheimer's Disease

L. Guo[1], M. Pahlitzsch[#, 1], F. Javaid[#, 1] and **M.F. Cordeiro[*, 1, 2]**

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Abstract: Alzheimer's disease (AD) is the most common cause of dementia globally. The prevalence has increased dramatically with an aging population. Although considerable progress has been made over the last few decades in understanding the pathophysiology of AD, early and accurate diagnosis of the disorder is still a formidable challenge, and there is currently no effective treatments available to slow down disease progression. The fundamental issue on this disadvantage is largely due to a lack of reliable biomarkers for neurodegeneration in the brain. However, mounting evidence has shown that except the brain, the eye, particularly the retina, is also affected in AD. Because of its transparent nature and ease of accessibility, the eye can serve as a 'window' into the brain. Advanced imaging technologies enable observation of changes in the retina in real time, *e.g.* measurement of thickness of the retinal nerve fibre layer (RNFL) by coherence tomography (OCT), detection of changes in the optic nerve head (ONH) by confocal scanning laser ophthalmoscopy (cSLO), and monitoring of retinal neuronal apoptosis by DARC (Detection of Apoptosing Retinal Cells). In addition to the ocular structural changes in AD patients, similar pathological mechanisms identified in the brain have also been established in the retina, including increased amyloid-ß (Aß) deposition and tau pathology. Furthermore, AD-related changes in the retina have also been observed in eye diseases, including glaucoma and age-related macular degeneration (AMD), and targeting of Aß has been demonstrated to be neuroprotective for those eye diseases. This review focuses on the recent advances in ocular changes, particularly retinal neurodegeneration in AD, discusses pathological similarities between AD and eye diseases, and highlights the potential of retinal imaging in identification of promising biomarkers for early AD.

Keywords: Aß, Alzheimer's disease, AMD, DARC, Glaucoma, Retinal imaging, Retinal neurodegeneration, Tau.

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Atta-ur-Rahman (Ed.)

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by progressive cognitive decline and memory impairment [1]. AD is the most common cause of dementia, and there is currently no known treatment to delay its progression. It has been estimated there is 44 million people affected by dementia globally in 2010 with the cost of over US$600 billion, and the prevalence of AD worldwide is anticipated to triple by 2050 [2]. The hallmark lesions in AD are amyloid-ß (Aß) plaques and neurofibrillary tangles (NFTs), composed of tau protein, both causing neuronal degeneration and synaptic failure in the brain [3, 4]. Although the first case of AD was reported a century ago [5], early and accurate diagnosis of the disease still remains a formidable challenge.

Currently, the diagnosis of AD is based on clinical neurological and psychiatric examinations in addition to distinguishing pathological features from the medical and family history [6]. Over the last decade however, neuroimaging of biomarkers has been investigated in multicentre clinical trials worldwide [7, 8], aimed to find the validated tools for the early diagnosis of AD, the tracking of disease progression, and the evaluation of novel therapeutic strategies. The outcomes have been encouraging, and a recent comprehensive review from the Alzheimer's Disease Neuroimaging Initiative (ADNI) [8] has reported that cerebrospinal fluid (CSF) biomarkers, ß-amyloid 42 and tau, as well as amyloid positron emission tomography (PET) may reflect the earliest signs in AD and that longitudinal magnetic resonance imaging (MRI) is proved most highly predictive of disease progression and has great potential for improving novel drug development, but none of them is a mature biomarker yet [9 - 11].

The main difficulty in the early detection of AD is possibly the incapacity of direct observation of microscopic and cellular changes in life time in the brain [12]. This however, is easily performed non-invasively through the medium of the eye [13 - 16]. Evolving imaging techniques now enable direct detection of changes in the retina and the optic nerve disc, as well as changes in single retinal neurons and their axons. Mounting evidence suggests that there are visual and ocular manifestations of AD, thus supporting the concept that the eye is indeed a window to the brain [17 - 21]. Tracking of retinal changes in real time may further facilitate improved understanding of the neuropathological mechanisms in AD, which implicates development of diagnostic methodologies in addition to providing parameters in assessment of novel therapeutic strategies.

THE RETINA – AN INTEGRAL PART OF THE BRAIN

The retina is part of the brain in the central nervous system (CNS) Embryologically, both the retina and the brain are derived from the neural tube, a

precursor of the CNS during development. Anatomically, the retina connects to the brain through a collection of fibres – the optic nerve. The retina converts light into nerve signals to allow us to see the world. The neural retina consists of three layers of nerve-cell bodies which are connected by two layers of plexiform (Fig. **1**). The nerve-cells in the most outer layer are the light receptors called photoreceptors (the rods and cones) and that in the most inner layer are the retinal ganglion cells (RGCs). The middle layer of the retina contains three types of nerve cells which are bipolar cells, horizontal cells, and amacrine cells. On the layer of RGCs, their axons run across the surface of the retina, collect in a bundle at the optic disc, and leave the eye to form the optic nerve.

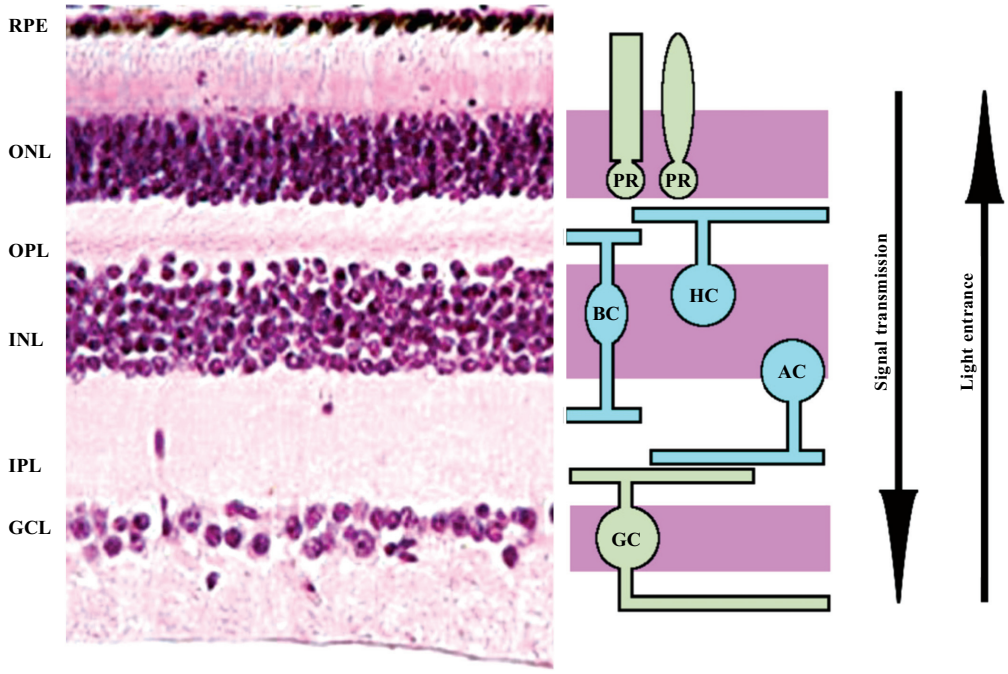

Fig. (1). Retinal structure and light transmission. The retina consists of three layers of nerve-cell bodies and two layers of plexiform, which are responsible for the transmission of light signals from the retina to the brain. The nerve-cells in the most outer layer (outer nuclear layer, ONL) are the light receptors called photoreceptors (PR) and that in the most inner layer (GCL) are the retinal ganglion cells (GC). The middle layer of the retina (inner nuclear layer, INL) contains three types of nerve cells - bipolar cells (BC), horizontal cells (HC), and amacrine cells (AC). On the layer of RGCs, their axons pass across the surface of the retina, collect in a bundle at the optic disc, and leave the eye to form the optic nerve. The light enters the eye from the inner surface of the retina *via* GCL, and passes through all the layers before being detected by PR (light entrance arrow). PR transduces the visual signals to GC *via* the three intermediate neurons and their synapses in the two platforms (IPL and OPL) (signal transmission arrow). RPE: retinal pigmental epithelium.

Light enters the eye and gets onto the inner surface of the retina after passing through the transparent media, *i.e.* the corner, lens and vitreous. Light then further

CHAPTER 4

Pathophysiology of Alzheimer Disease: Current Drug Therapy

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Abstract: Alzheimer's disease (AD) is a neurodegenerative age related disease in which patients of age 65 or more suffer from memory impairment problems. This disease is related to the nervous system degradation and various pathophysiological conditions have been identified such as formation of β-amyloid and plaques, nerve degeneration, neurotransmitter depletion, accumulation of toxins, oxidative stress and inflammation. Local RAS system in the brain is different from vascular RAS and play an important role in pathophysiology of AD. RAS system modulates inflammatory processes, neurotransmitter activity and amyloid and plaque formation. Angiotensin II, a vasoconstriction peptide of RAS system also induces neuronal cell loss by the process of cell senescence. Genetic polymorphism is also an important factor for pathophysiology and treatment of AD. No treatment is available which can eradicate AD completely; only prophylactic treatments are available which gives only prophylactic relief. Treatments are given which improve the pathophysiological condition of the disease and restore the brain cells activity. Treatment approach includes prevention of β amyloid and plaque formation, restoration of neurotransmitter system, prevention of oxidative stress and inflammation. Other than allopathic medicines, traditional system of medicines also have number of herbs and plants which have the property of learning and memory improvement *via* different mechanism of actions.

Keywords: Alzheimer's disease, Angiotensin II, β amyloid, Dementia, Herbal treatment, Neurons, Renin Angiotensin System, Treatments.

INTRODUCTION

Older people often forget things like someone's name or misplace belongings. This kind of behavior is normal but forgetting how to get home, getting confused in places a person knows well, difficulty in collecting words and language understanding, asking questions again and again can be signs of a more serious

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Atta-ur-Rahman (Ed.)

condition known as dementia. The situation even can lead to irreversible loss of memory. Dementia can be of many types, Alzheimer being one of them is very critical. These above symptoms may be the initiation of Alzheimer's disease (AD). Alzheimer is type of chronic dementia starting with neuron degeneration and cause difficulty in thinking, psychological, behavioral, language and memory related problems. It's a progressive disease and symptoms appear slowly which worsen over time leading to complete memory loss [1]. It is mainly affecting peoples of above 65 years of age but it is not a normal part of aging. According to Alzheimer's association a recent report says about 5.4 million Americans are suffering from this disease out of which 5.2 million patients are of 65 age or older while 200,000 are under age 65 and its incidence increase with age. In America Alzheimer's prevalence in 1 in 9 persons this time and is expected to occurs a new case in every 33 seconds during the mid of this century [2]. World Alzheimer report 2015 shows that 46.8 million people are living with dementia worldwide and this doubled in every 20 years. The major impact of Alzheimer is in low to middle income countries and prevalence of this disease will increase to 68% by 2050 as compared to 58% in 2015 [3]. AD increase will be more in population of low income developing countries like China, India, and in south Asian and western Pacific. India is the most populous country with middle income and 2001 census showed that more than 76 million people of age 60 year and more live in India. The prevalence of AD in India varies from 1.02 to 3.36 per cent in 60-65 years age group and approximately 1.5 million of Indian population is affected by dementia and this is expected to increase by 300 percent in next four decades [4]. AD is a genetic disorder and genetic mutation of some genes such as amyloid precursor protein, presenilin-1 and presenilin-2 is the cause of the AD in majority of cases. But in most of the cases disease is not clearly transferred as genetic trait from one generation to other and without Mendelian pattern of inheritance.

PATHOPHYSIOLOGY OF ALZHEIMER'S DISEASE

AD is a type of dementia which starts with degradation of neuronal function and even can ultimately result in death. It is age dependent and its prevalence increase with age. Patients of age 65 or more are more prone to neuron related problems leading to AD. Many neurotransmitter systems and pathophysiological processes are identified to play a role in the pathophysiology of AD. Alzheimer occurs when nerve cells died or blocked by some plaques. Brain is made up of interconnected network of millions of neurons which collectively performs the functions of information storage and communication of stored information when needed such as memory, learning, thinking and senses such as hearing, vision, smelling and taste [5]. In AD, blockage in neurons interferes with these functions which may lead to damage to brain at macro and micro level. These factors either directly brain related or indirectly associated factors may interfere with functioning of

brain in several ways (Fig. **1**). At macro level loss of brain tissue results in change in structure of brain. Hippocampus part of brain cortex is supposed to be involved in memory related processes and loss of cortex neurons causes loss of memory. Memory loss is the sign of initiation of AD. The brain atrophies after loss of neurons are occupied by cerebrospinal fluid. At later stages brain atrophies spread to areas of brain responsible for controlling speech, reasoning, sensory processing and though. Micro level processes may directly harm nerve cells which are responsible for reduction in activity of brain cells. The neuron degenerative processes are listed below [6, 7]:

- Neuronal cells death
- Development of Beta amyloid plaques between nerve cells
- Development of Tangles by protein precipitation inside the neurons

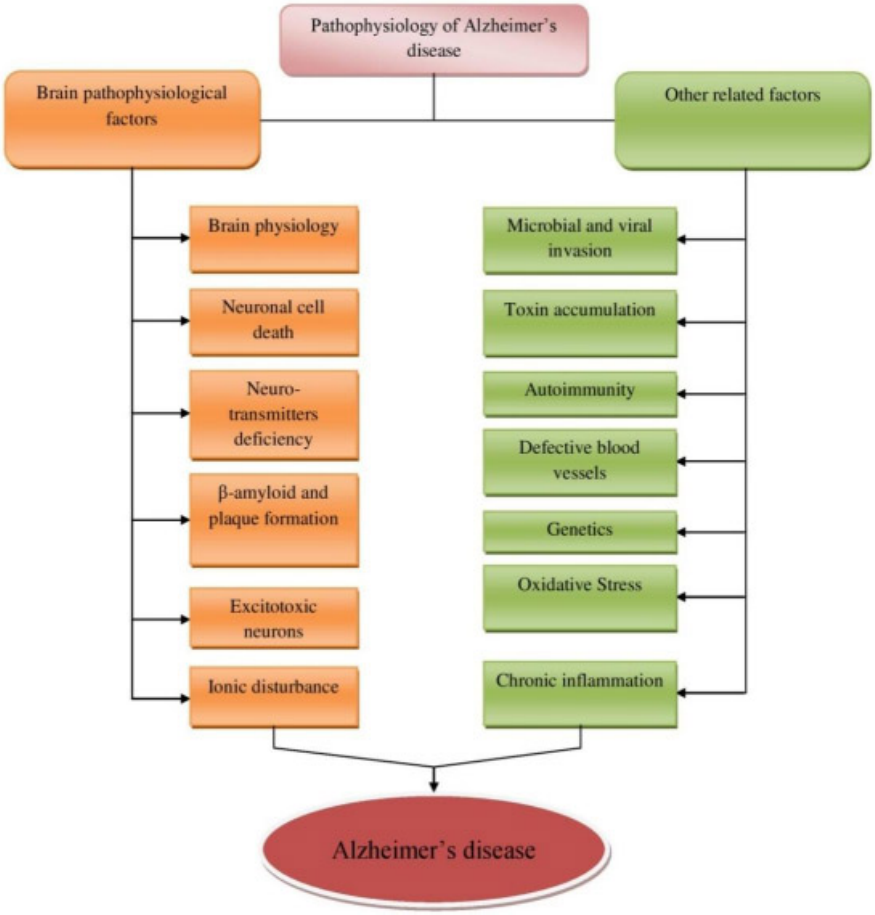

Fig. (1). Pathophysiological process of Alzheimer's disease.

CHAPTER 5

Biological Mass Spectrometry for Diagnosis of Alzheimer's Disease

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Abstract: Mass spectrometry (MS) has advanced the diagnosis of Alzheimer's disease. In the present chapter, applications of mass spectrometry for the diagnosis of Alzheimer's disease were summarized. Mass spectrometry showed new exciting results, offered high sensitivity (in the femtomolar range), showed high selectivity, has better accuracy, offered high throughput, were extremely rapid (the entire process required few minutes) and can be used for quantitative, qualitative and imaging. Recent mass spectrometry techniques based on nanotechnologies replaced some of the classical MS techniques. These new technologies improved the diagnosis of Alzheimer's disease. Mass spectrometry covered wide range of Alzheimer's disease biomarkers such as amyloid β, total tau protein (t-tau), α-synuclein, posttranslational modification (phosphorylated tau protein, protein S-nitrosation (SNO), racemization, methylation, chlorination and others) and metals ions. From the analytical point of view, mass spectrometry offered detection of large number of biomarkers in a single test. Mass spectrometry has significantly advanced Alzheimer's diagnosis of living patient and postmortal. Monitoring Alzheimer's biomarkers using MS is very promising for the diagnosis in early stages of the disease. However, the proper interpretation of MS profiling is critical and requires careful investigations. Furthermore, the identification of the biomarkers using MS profile is affected by many key variables that have to be considered during the analysis.

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Keywords: Alzheimer's disease, Amyloid β, Biomarkers mass spectrometry imaging, Mass spectrometry, Tau protein.

INTRODUCTION

Mass spectrometry (MS) is an attractive and invaluable analytical technique that can be applied for wide analytes [1, 2]. Mass spectrometry (MS) measured the mass to charge ratio (*m/z*) of ions to identify and quantify the target molecules. It has been applied for many fields such as proteomics [3, 4], metabolomics [5], biology [6], nanotoxicology [7 - 10], and others [11 - 14]. It has advanced the field of molecular medicine and provided revolution in the diseases diagnosis. It has many subclass based on ionization methods. Thus, these techniques provided a practical analyzer for biomarkers, diagnosis and screening of many diseases. Mass spectrometry potentially outperformed the other traditional methods [15 - 17].

Mass spectrometry (MS) was used in diagnosis and screening for Alzheimer's disease [17 - 20], heart disease [21], inherited metabolic diseases [22], newborn-screening programs [23], inborn errors of metabolism [24], heart diseases and clinical proteomics [25], diabetes mellitus [26], and others [27 - 29]. Mass spectrometry is potentially promising in clinical chemistry for identification of disease's biomarkers [30]. Disease biomarkers can be identified by mass spectrometry analysis. The analysis can be in combination with separations techniques and identification is simple by using fingerprinting (Peptide Mass Fingerprinting, PMF) or peptide sequence tag (PST). Database of protein, peptide and other biomolecules biomarker can be used for further identification and confirmation.

Alzheimer’s disease is dementia type disease that belongs to neuropathological and neurodegenerative disorder affecting >5% of the population over the age of 65. Alzheimer’s disease affects the patient's memory, language, thinking, mood, and behavior (difficulty speaking, confusing about events, and walking). Alzheimer's disease is mainly pathological alterations in the brain of patients due to unknown reasons. It may be due to β-amyloid deposition and hyperphosphorylation of τ protein [31], oxidative stress [32], mitochondrial dysfunction [33], metal dyshomeostasis [34], and lipid dysregulation [35]. The main challenge of this disease is that their symptoms usually develop slowly. The symptoms become worse over the time and are enough to affect the daily tasks. Thus, early diagnosis of the disease is highly demanded. Among the different analytical techniques, mass spectrometry is promising for Alzheimer's disease diagnosis.

This chapter discussed the applications of mass spectrometry for the diagnosis of Alzheimer's disease. The requirements of the diagnosis in the early stages were discussed. The recent achievement of the disease diagnosis using mass spectrometry was reviewed. The examples cited here highlighted the contribution of mass spectrometry for Alzheimer's disease. Mass spectrometry offered several advantages such as fast diagnosis, high sensitivity, high selectivity, accurate and are easy to combine with other separation techniques.

Requirements of Alzheimer's Disease Diagnosis

There are several requirements for diagnosis and screening of Alzheimer's disease. The analysis should be (i) fast to analysis many organs, tissues and body samples in a short time; (ii) offer high accuracy to avoid errors and misconclusion; (iii) have high sensitivity to detect the disease in the early stages; (iv) offer high selectivity toward the target biomarker to give clear indication without any confusion; (v) sample preparation should show minimum loss of the biomarker or cause no artefacts; (vi) provide high resolution in order to analysis complex and real sample such as body fluids, organs or tissues; (vii) sample pretreatment such as preconcentration or separation method should be simple; (viii) the device should be simple to handle, easy to clean and can be recondition fast for next measurement and (ix) interfering species cause no effect on the separation procedure.

Among different analytical techniques, mass spectrometry fulfilled almost all the previous criteria as discussing in this chapter. Thus, it has been applied for many diseases such as Alzheimer's disease. Mass spectrometry consists of five parts as shown in Fig. (**1**); sample inlet, sample analyzer, mass analyzer that separate ions based on *m/z*, detector and vacuum system [36 - 41]. The investigated species are ionized in the mass analyzer before the separation based on mass to charge in the analyzer. The ionized species are detected in the detector and a plot of the intensity *versus* the mass to charge ration is obtained. To avoid the lost of the ions charge, vacuum is used.

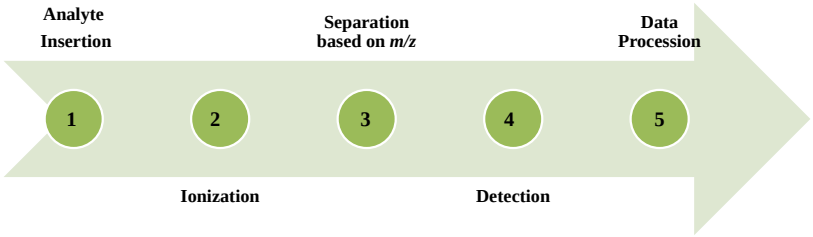

Fig. (1). Mass spectrometry consists of five parts; sample inlet, ion source, mass analyzer, detector and high vacuum.

CHAPTER 6

The Structure-Activity Relationship of Melanin as a Source of Energy Defines the Role of Glucose to Biomass Supply Only, Implications in the Context of the Failing Brain

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Abstract: Decreasing brain metabolism is a substantive cause of cognitive abnormalities in Alzheimer´s Disease (AD), although this hypo-metabolism is poorly understood, *i.e.* is not known if it is primary or secondary. Neuron ion homeostasis and thereby synapsis are a crucial and highly energy demanding processes, and one of the hallmarks of AD is the loss of synapsis in defined regions of the brain. Until today, alterations in mitochondrial energy supply have been considered the main concern due to in aging rat neuron model, mitochondria are both chronically depolarized and produce more reactive oxygen species with age. Thereby, impoverished mitochondrial function has been actively studied trying to reverse and recover ATP generation. Today, after more than 100 years that Alois Alzheimer described Augusta D., patients still die in the same way, in spite multiple treatments, multiple theories, multiple studies and unfruitful clinical trials.

We believe that the unraveling of the unsuspected intrinsic property of melanin to transform visible and invisible light into chemical energy through the dissociation of the water molecule, as chlorophyll in plants, will mark a before and after, this is: a new frontier, in the understanding and treatment of the nightmare of the XXI century: Alzheimer´s Disease.

Keywords: Alzheimer, Energy, Hydrogen, Light, Melanin, Neurodegeneration, Synapsis.

INTRODUCTION

Alzheimer´s Disease is characterized by a progressive deterioration of cognitive function with memory loss. The most affected regions of brain in AD include the

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Atta-ur-Rahman (Ed.)

basal forebrain, amygdaloidal body, hippocampus, entorhinal cortex neocortex, and brain stem nuclei [1] (Fig. **1**). Most cases are sporadic with no known genetic linkage.

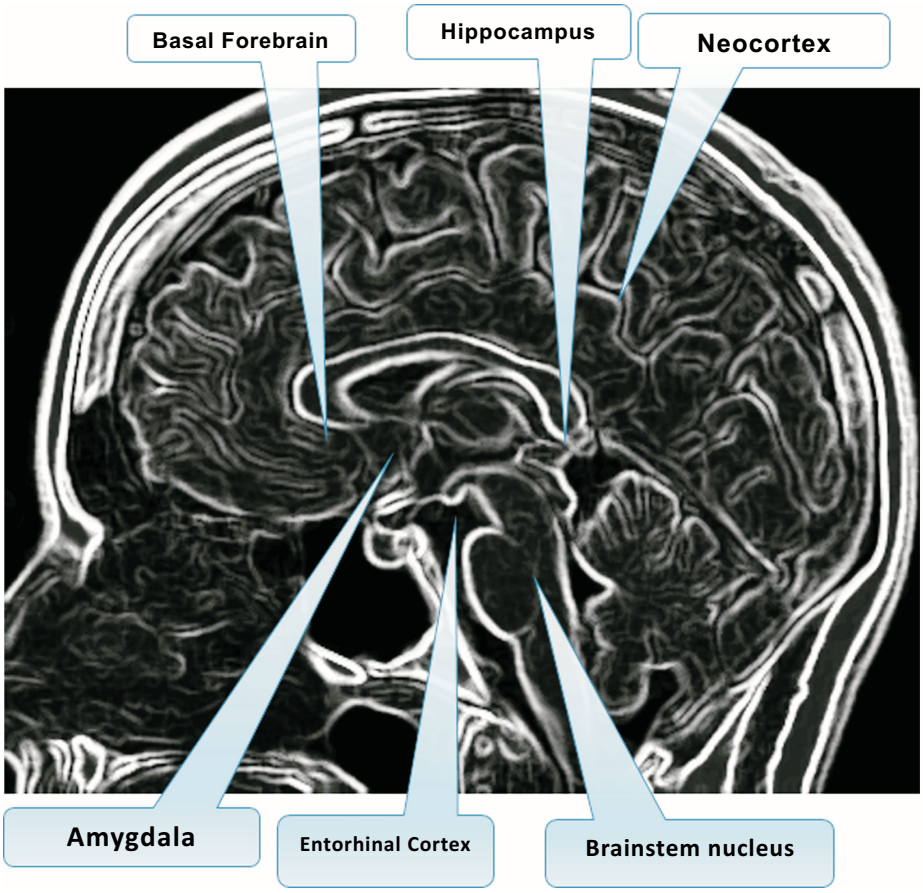

Fig. (1). Arrows show approximate location of the brain tissue that seems especially affected in AD, functional and anatomically.

Despite the many existing histopathological descriptions to date, the cause of Alzheimer's Disease remains in the incognito [2]. The presence of extracellular β-amyloid peptide-containing neuritic plaques, intracellular neurofibrillary tangles (NFT) and the loss of synapses in more or less defined regions of the brain are the hallmarks associated with AD in post-mortem pathology.

Amyloid (starch-like) deposits contain extremely insoluble protein fibrils with similar morphologic features with many, if not all, neurodegenerative disorders [3]. These 80-150 Å length fibrils comprise many different proteins with no obvious sequence similarity. Abnormal protein aggregation characterize

Alzheimer´s Disease (AD), Parkinson´s Disease (PD), Creutzfeld-Jakob Disease (SP, Spongiform Encephalopathy, prion protein deposits), Motor Neuron Diseases, the large group of polyglutamine disorders (tri-nucleotide repeat diseases), including Huntington´s Disease, as well as diseases of peripheral tissue like Familial Amyloid Polyneuropathy (FAB) [4], Amyotrophic Lateral Sclerosis, and Tautopathies (Progressive Supranuclear Palsy, Pick´s disease, corticobasal degeneration, Familial Frontotemporal Dementia, Parkinson-linked to chromosome 17).

Abnormal protein-protein interactions that result in the formation of intracellular and extracellular aggregates of proteinaceous fibrils are a common neuropathological feature of several neurodegenerative diseases. It has been suggested that abnormal protein-protein interactions and/or the lesions that result from the aggregation of these proteins could play a mechanistic role in the dysfunction and death of neurons in several common (and rare) neurodegenerative diseases.

Lewy bodies (LB) are intracytoplasmic neuronal inclusions observed very frequently in PD, however, they also occur commonly in the brains of patient with clinical and pathological features of AD.

Numerous cortical LBs are found in Dementia with Lewis bodies (DLB), which is similar to AD clinically, but pathologically distinct NFTs and senile plaques (SPs) are rare or completely absent in DLB brains. The precise molecular composition of LBs is unclear, also their role in the degeneration of neurons in PD, and DLB.

Synuclein was identified in rat brain in 1991, subsequently, a fragment of the 140 amino acid long human α-synuclein protein was reported to be present in some amyloid plaques of AD brains. The normal functions of α-synuclein in neurons are poorly understood. The biochemical changes that predispose this normally soluble and randomly structured α-synuclein protein to aggregate or interact aberrantly with itself or other proteins, are unknown.

The widespread presence of α-synuclein in perikaryal LBs, and in dystrophic neuronal processes of brains of patients with PD and DLB, and immunohistochemical studies with antibodies to α-synuclein reveal a much more extensive network of dystrophic processes, suggesting a generalized failure more than a punctual alteration.

The state of the art in relation to pathological findings and the clinical picture in AD, PD and other neuro-degenerations are has become so intricate, that even is has failed to discern if the correlation and co-location of fibrillar proteins and the affected tissue suggests that fibrillization contributes to cell death or if it is an

CHAPTER 7

Neuro-protective Properties of the Fungus *Isaria japonica*: Evidence from a Mouse Model of Aged-related Degeneration

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Abstract: *Isaria japonica* (IJ), is an entomopathogenic fungus that is grown on pupae of the silkworm *Bombyx mori* for its medicinal properties. Its extracts have potential neuro-protective effects. An extract reversed astrogliosis in the CA3 area of the hippocampus of aged mice. The CA3 area is responsible for spatial pattern association and completion, detection of novel situations, and short-term memory. This finding led us to the development of treatments to improve age-related impairment of patients with Alzheimer's disease (AD). Acute and subchronic toxicity and chemical profiling of the extract were conducted for the assessments of medical use. We are now evaluating preclinical trials with AD patients. For the diagnosis of AD, magnetic resonance imaging (MRI) enabled the detection of the previously invisible pathological alterations in a mouse sclerosis model with autoimmune encephalomyelitis. Magnetic resonance spectroscopy (MRS) showed that demyelination regions in some multiple scrlosis (MS) patients had increased lactic acid content, suggesting the presence of ischemic events. These results show that products derived from IJ may prevent or reduce the impact of dementia, especially AD, and MRI and MRS could lead widely to the diagnosis of neurological diseases.

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Keywords: Aged brain, Alzheimer's disease, Astrogliosis, Dementia, Entomopathogenic fungus, *Isaria japonica*, Magnetic resonance imaging and magnetic resonance spectroscopy analyses, Multiple sclerosis, Nuclear magnetic resonance spectroscopy analysis.

INTRODUCTION

Under natural conditions, the entomopathogenic fungus *Isaria sinclairii* (= *I. cicadae*) grows on larvae of the cicada, *Meimura opalifera* Walker (*Hemiptera*: Cicadidae). Following the discovery that the culture broth of this fungus had potent immunosuppressive activity [1], a novel synthetic compound (FTY720), with lower toxicity and *in vitro* and *in vivo* immunosuppressive activity, was developed from a fungal metabolite as a lead compound, myriocin (= ISP-1) [2]. This compound, named fingolimod, has opened up a new approach to the treatment of MS [3].

Keeping in mind since the brain disease-treated agents are originated from entomopathogenic fungi, we have learnt that *Ophiocordyceps, Cordyceps* and *Isaria* spp. are traditionally used as to treat cancer, diabetes, cardiovascular diseases, and neural disorders, albeit without good scientific evidence [4 - 8]. The price of natural products and large-scale harvesting of wild fungi pose problems [9, 10]. Biopharmaceuticals derived from those fungi are anticipated, but the effect of 3'-deoxyadenosine, a cordycepin with potential anti-cancer first described in 1950, has not been tested in clinical trials [11].

Many studies have only shown about pharmaceutical effects of medicinal mushroom and fungi on the experimental animals, but medicinal uses for human have made very little progress so far [12]. There were anti-fatigue ability and higher endurance with the supplement of *Ophiocordyceps* (= *Cordyceps*) *sinensis* [13] and for patients with advanced liver disease and inoperable tumors and treated with 4 natural agents that included *O. sinensis*, the tumor was found to decrease in size, the tumor marker levels decreased substantially, and the patients survived comfortably [14]. Yet, more experiments are needed to demonstrate sufficient data on the efficacy and safety of entomopathogenic fungi to find new sources for drug discovery [12].

Thus, other sources that do not contribute to the loss of natural entomopathogenic fungi or depend on market forces are being investigated. We have grown *I. japonica* (IJ = *Paecilomyces tenuipes*) sourced from a mountain field in Fukusima Prefecture, Japan, on dried silkworm (*Bombyx mori*) pupae left over from silk extraction (Fig. **1**) [15], obviating the need for wild harvesting.

Fig. (1). Synnemata and conidia of IJ cultured on dried pupae of *Bombx mori.*

To evaluate the effects of entomopathogenic fungi, mice aged by treatment with D-Galactose in an aging model for the brain and dosed orally with a hot-water extract of *O. sinensis* showed a significantly reduced decline of spatial learning and memory ability [16]. The hot-water extract of *O. sinensis* also prevented structural changes in the hippocampus of aged mice and shortened the mount latency of castrated rats. These findings indicate that the hot-water of *O. sinensis* has an anti-aging function. Therefore, we tested IJ extract (IJE) for similar effects.

We found that IJE improves nerve function in aging mice and may lead to the development of treatments for Alzheimer's disease (AD) [15]. This comprehensive review discussed neural improvement in the aged brain; nuclear magnetic resonance (NMR) analyses of IJE; towards a goal of complementary and alternative medicines /or medicines originated from the entomopathogenic fungus, and the potential use of MRI and MRS for the diagnosis of neurological diseases.

IJE Improves Nerve Function in Aged Mouse Brain

IJE reduced astrogliosis and improved memory deficits are the characteristics of serious disorders of the central nervous system such as AD and MS [17, 18].

1. Neuroprotective Effects of IJE

In many studies, D-Galactose induced [19 - 21] or SAMP8 [22] mice have drawn attention in research on dementia owing to their characteristic learning and memory deficits in old age. D-Galactose treatment induces learning and memory impairment but causes no neuromuscular dysfunction, and it is effective for testing the neuroprotective effects of chemicals. Thus, chronic systemic exposure of mice to D-Galactose is a useful model for analyzing the mechanisms of neurodegeneration and neuroprotective drugs and agents [21]. In accordance with

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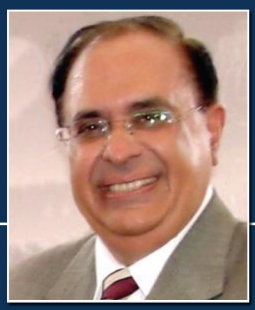

PROF. DR. ATTA-UR-RAHMAN, *FRS*

Atta-ur-Rahman, Ph.D. in organic chemistry from Cambridge University (1968), has 1020 international publications in several fields of organic chemistry including 727 research publications, 37 international patents, 68 chapters in books and 188 books published largely by major U.S. and European presses. He is the Editor-in-Chief of eight European Chemistry journals. He is Editor of the world's leading encyclopedic series of volumes on natural products "Studies in Natural Product Chemistry" 50 volumes of which have been published under his Editorship by Elsevier during the last two decades.

Prof. Rahman won the UNESCO Science Prize (1999) and was elected as Fellow of the prestigious Royal Society (London) in July 2006. He has been conferred honorary doctorate degrees by many universities including (Sc.D.) by the Cambridge University (UK) (1987). He was elected Honorary Life Fellow of Kings College, Cambridge University, UK, conferred the TWAS (Italy) Prize and the Austrian government has honoured him with its high civil award ("Grosse Goldene Ehrenzeischen am Bande") (2007). He is Foreign Fellow of Chinese and Korean Academy of Sciences, Foreign Fellow of the Chinese Chemical Society and former President of Pakistan Academy of Sciences.