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(CNS and Neurological Disorders)

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PREFACE

Studying brain physiology and development is a leading neuroscience strategy not only to illuminate the general understanding of brain structure and function but also to make progress against neurodegenerative disorders that are devastating the healthy aging.

The volume 11 of our book series *Frontiers in Clinical Drug Research - CNS and Neurological Disorders* introduces the subject of neurodegeneration by outlining the pathophysiology genetics, and environmental factors. This book besides providing a clear overview of the neurodegeneration and addiction process also introduces the readers to a new synthesis of ideas. To contextualize the research for the general readers, it also provides a brief introduction to the pharmacological and non-pharmacological approaches to treat the commonest neurodegenerative and addictive disorders. This book takes interested beginners on a journey from a cold start to a grasp of neuroscience's best line of research. The current volume integrates the work of neurobiologists into a coherent account of the nature of neurodegenerative and addictive disorders and their treatment.

For instance, **Chapter 1** highlights the multi-target directed ligands candidate prototypes inspired mostly by natural products to treat some of the most studied diseases, namely, Parkinson's Disease, Alzheimer's Disease, and Huntington's Disease, as well as amyotrophic lateral sclerosis. **Chapter 2** discusses the role of psychological and neurological factors as well as genetics and neurobiological mechanisms to review the drugs used for relapse prevention to treat addiction to nicotine, alcohol, or illicit drugs. **Chapter 3** summarizes the neuroprotective properties of cinnamic acids and their derivatives in light of their mechanistic aspects to treat various neurodegenerative disorders. **Chapter 4** reviews the role of phytosome in the targeted delivery of natural compounds across the blood brain-barrier to improve the efficacy, and bioavailability of Alzheimer's drugs. **Chapter 5** glances at clinical trials investigating non-pharmacologic approaches, such as physical activity to improve the symptoms of Alzheimer's Disease.

Briefly, this volume is the definitive guide to common neurodegenerative diseases that affect humans. The book covers the mechanisms of some of the most well-known neurodegenerative and addictive diseases, their biomarkers, neuropharmacology, and emerging treatment strategies.

We are grateful for the timely efforts made by the editorial personnel, especially Mr. Mahmood Alam (Director Publications), and Ms. Asma Ahmed (Senior Manager Publications) at Bentham Science Publishers.

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CHAPTER 1

Multi-functional Ligands and Molecular Hybridization: Conceptual Aspects and Application in the Innovative Design of Drug Candidate Prototypes for Neurodegenerative Diseases

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Abstract: The rapid increase in the incidence of dementia has enormous socio-economic impacts and costs for governmental health systems all over the world. Despite this, finding an effective treatment for the different types of neurodegenerative diseases (NDs) so far represents a challenge for science. The biggest obstacles related to NDs are their multifactorial complexity and the lack of knowledge of the different pathophysiological pathways involved in the development of each disorder. The latest advances in science, especially those related to the systems biology concepts, have given new insights for a better comprehension of such multifactorial networks related to the onset and progression of NDs, and how Medicinal Chemists could act in the search for novel disease-modifying drug candidates capable of addressing the multiple pathological factors involved in neurodegeneration. The multi-target directed ligands (MTDLs) concept has captivated and opened new windows for the creativity and rationality of researchers worldwide in seeking innovative drug candidates capable of modulating different molecular targets by a single multifunctional molecule. In fact, in

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the last two decades, thousands of research groups have dedicated their efforts to the use of molecular hybridization as the main tool for the rational design of novel molecular scaffolds capable of expressing multi-target biological activity. In this way, this chapter addresses the most recent pathophysiological hallmarks of the most high-impact NDs, represented by Alzheimer's, Parkinson's, Huntington's diseases, and amyotrophic lateral sclerosis, as well as the state-of-art in the design of new MTDLs, inspired mostly by natural products with improved druggability properties.

Keywords: Molecular Hybridization, MTDLs, Multi-target Directed Ligands, Multifunctional Drugs, Neurodegenerative Diseases, Rational Drug Design.

INTRODUCTION

Neurodegenerative diseases (NDs) are recognized as a group of incurable, severe, progressive and disabling chronic neurological pathological conditions, with great social and economic impacts worldwide, representing one of the biggest current challenges for all sciences focused on human health [1 - 6]. Currently, due to their high incidence and epidemiological impact, NDs have Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS) as their main representants, as attested in the scientific literature for the enormous efforts in drug discovery, pharmacological and biological projects addressed for the discovery of novel drug candidate, innovative therapeutics and a continuous search for a better comprehension of their pathophysiological features. Today, it is estimated that about 50 million people have some type of dementia worldwide and that this number is increasing by 10 million new cases every year [7], and medical treatments are onerous and are predicted to amount to 2 trillion US dollars in 2030 [8].

These four main types of NDs have been currently recognized as chronic inflammatory pathologies, also characterized by multiple interconnected physiological, biochemical, and cellular changes, along with chemical mediators operating concurrently and caused by the same or different pathways [5, 6, 9 - 12]. During the last decade, we have observed considerable efforts and investments from Governmental and non-Governmental sources, resulting in major advances in different fields of biological and chemical sciences and the consequent establishment of new insights into the knowledge of how complex and multifaceted the pathophysiological hallmarks of NDs are. Despite the efforts of research centers to discover new drugs for NDs, many have failed in clinical trials [8].

Aging is currently well accepted as one of the main risk factors related to the NDs onset, but why are some people more susceptible than others to be affected by ND? The answer to this question seems to be related to neuronal cells'

vulnerability, which states that different neuronal cells of the central and peripheral nervous systems are exposed and affected differently by environmental and age-related changes, resulting in a time-dependent decline in cognition, memory, sensory, and motor coordination [5, 11, 13 - 16]. Meanwhile, which nervous region and type of neurons are most affected by aging during life is an individual factor. Despite aging, all these NDs are also related to genetic, epigenetic, and environmental factors. Rare cases of early onset of AD, PD, and ALS are determined by mutations in specific genes, leading to the occurrence of symptoms at 30-40 years old. In general, most cases of dementia are associated with alterations in neuronal physiology as an effect of protein misfolding, imbalance in oxidative processes, neuroinflammation, and mitochondrial dysfunction [6, 12, 13, 17 - 21]. Recent progress in neurobiology has decisively contributed to clarifying how specific neurons, in specific brain regions and under specific conditions, are more susceptible to molecular, morphological, and functional changes, leading to neurodegeneration and, in turn, how this selective neuronal vulnerability could be the basis of the changes observed in the behavior of neuronal cells, their susceptibility, and responsiveness to aging differently than other non-neuronal cells. Indeed, there is enough evidence that brain cells experience much more exacerbated effects due to oxidative stress (OS), energy supply perturbation, and deleterious effects of protein deposition. Moreover, as age advances, different populations of neurons in different brain regions seem more vulnerable to these biochemical changes, leading to individual responses to and determining which one will develop or not ND, consequently to genetic and environmental factors [5, 6, 11, 13, 16].

Considering the multifactorial related to NDs, their onset, progression, and severity, a better understanding of the relatively low efficacy of current disease-modifying treatments based on selectively targeted drugs is possible. In this context, and due to the high adaptive ability of our organism and the many concurrent biochemical pathways to be modulated for a single pathology, the most recent literature data point out that it is unavoidable to adopt a new concept for the rational design of drug candidates for the treatment of such multifactorial disorders [1, 4 - 6, 9, 22, 23]. Thus, the multi-target directed ligands (MTDLs) have emerged as a polypharmacology-based strategy for drug design, and it has called special attention from the scientific community [8].

THE MTDLS PARADIGM AND MOLECULAR HYBRIDIZATION (MH) AS A TOOL IN DRUG DESIGN

Considering the multitude of interconnected cellular and biochemical factors associated with the onset, development, and pathophysiological complexity of NDs, and the lack of efficacy of the current chemotherapeutical practices, it

CHAPTER 2

Drugs For Relapse Prevention in Addiction: Review of Psychological and Neurological Factors, Genetics and Neurobiological Mechanisms

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Abstract: Behavioral and substance addictions share more similarities than differences in etiological, phenomenological, and clinical presentations. Interactions between the variables of predisposing (*i.e.*, neurobiological and psychological constitutions) and moderating (*i.e.*, coping style and cognitive and attentional biases), as well as variables of mediating (*i.e.*, affective and cognitive reactions to situational triggers) in combination with reduced inhibitory control may accelerate or reduce the developing of specific versions of model for addictive behaviors. Around 50% individuals' variability in becoming addicted to substance (nicotine, alcohol, or illicit drugs) is attributable to genetic factors. Genetic variations to addiction susceptibility and environmental factors such as stress or social defeat also alter brain-reward mechanisms impart vulnerability to addiction. The emergence and maintenance of addiction might be the consequences of chronic exposure to drugs remodeling the chromatin structure including FosB, Cdk5, G9a, and BDNF around genes. Only few drugs for substance use disorders (SUDs) are approved by the FDA, But QSP approaches provide valuable strategies for designing novel prevention or treatment towards drug addiction. Conjugate vaccines and monoclonal antibodies treatments generating high-affinity anti-drug IgG antibodies neutralizing drug doses in the serum might lead the immunotherapy for SUDs in the future.

Keywords: Addiction, Alcohol Use Disorder (AUD), Brain reward system (BRS), Conjugate vaccine, Genome-wide association study (GWAS), Monoclonal antibodies, Nicotine, Opioids Use Disorder (OUD), Quantitative systems pharmacology (QSP).

INTRODUCTION

The term addiction can be traced to Roman law according to the Oxford English

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Dictionary in page 24-25. From behavioral neuroscience, epidemiology, genetics, molecular biology, pharmacology, psychology, psychiatry to sociology, the study of addictive behavior is interdisciplinary [1]. "Addiction" reflecting individuals in pursuing reward and/or relief by substance use and behaviors, it is also defined by the American society of addiction medicine as a chronic disease of brain reward, motivation, memory and related circuitry. Addiction is included as a category by Diagnostic and Statistical Manual of Mental Disorders and contains both substances use disorders and non-substance use disorders [2]. Expert explained the Syndrome Model of Addiction in a revised view that an object of addiction can be a drug or drug-free activity. And the drug or activity must shift a person's subjective experience in a desirable direction (feeling good or better) for addiction to develop.

The characteristics of addiction are behavioral control impairment, craving, to consistently abstain inability, and diminished recognition of one's behaviors and interpersonal relationships. Addiction ranges from substance use disorder to addictive behaviors. Addictions involve substance (alcohol, tobacco, opioids, prescription drugs, cocaine, cannabis, amphetamines, hallucinogens, inhalants, phencyclidine and other unspecified substances [3 - 11]) are psychological and those not involving a substance are behavioral (food eating, sex, pornography, using computers/ internet, playing video games, working, exercising, spiritual obsession, pain, cutting, shopping [12 - 24]).

Scientific advances in brain-imaging technologies and genetic researches suggest that specific substance or behavioral addiction is less important than previously believed. Instead, addiction acts functionally between a person and an object or activity. The object or activity with addiction becomes increasingly more important [25] and ultimately, addiction become complex struggle between acting on impulse and resisting that impulse [26].

PSYCHOLOGICAL AND NEUROLOGICAL RISK FACTORS OF BEHAVIORAL ADDICTION

Behavioral Addiction

Behavioral Addiction and Substance Addiction

A core defining concept of addiction is diminished control. Despite knowledge of adverse consequences, behaviors or ingesting psychoactive substance producing short-term reward engender persistent behavior, *i.e.,* diminished control over the behavior. The non-substance or "behavioral" addictions, with syndromes analogous to substance addiction in the conception, but with a behavioral focus other than psychoactive substance ingestion [27, 28]. In fact, addiction of

behavioral and substance share more similarities than differences in etiological, phenomenological, and clinical presentations [29].

Not all disorders characterized by impulsivity considered to be behavioral addictions. Behavioral disorders of pathological gambling or kleptomania, classified as impulse control disorders by Diagnostic and Statistical Manual, 4th Edition (DSM-IV-TR) have similarities to substance addictions. Other impulse control disorders like compulsive shopping, pathologic skin-picking, sex addiction, excessive tanning, computer/video game playing, and internet addiction, *et al.*, have been planned for inclusion in the DSM-V.

Behavioral Addiction and Addictive Behavior

Addiction producing pleasure and providing escaping from internal discomfort, is characterized by powerlessness to control behaviour and unmanageability of the behaviour continuation despite knowing significant negative consequences [30]. The object of behavioral addictions (BAs) can be any behavior that could produce pleasure and provide relief. Gambling disorder (GbD) and gaming disorder (GmD) are two currently recognized in international classifications of BAs. GbD was the first acknowledged BA in the "Substance-related and addictive disorders" section of the DSM-V in 2013. The second acknowledged BA defined in 2018 in the eleventh edition of the International Classification of Disease (ICD-11) was GmD in section of "addictive behavior" [31]. Sexual addiction (SA), eating addiction [32], excessive exercise [33], kleptomania [34], or shopping addiction are other pathological behaviors are often reported as BAs in the literature.

Neurobiological Theories of Behavioral Addiction

The four neurobiological theories of addiction help the construction and understanding of addiction theory.

Learning theory. Learning theory assumed that action-outcome learning and stimulus-response or 'habit' learning are two learning processes relevant to understanding addiction [35]. Theory hypothesis that stimulates-response learning occurs with instrumental action-outcome learning parallelly, but eventually dominates behavioral output with extended training.

Dysregulation theory. Addiction is the pathology outcomes of allostatic mechanism with the natural rewards circuits. Dysregulation theory believed addiction is brain reward systems dysregulation in the increasing spiraling progressively into a circle of compulsive use and loss of control. There are different reinforcement sources, neuro-adaptive mechanisms and neurochemical changes to the brain reward circuits system are involved in this dysregulation. The

CHAPTER 3

Neuroprotective Activities of Cinnamic Acids and their Derivatives

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Abstract: Neurodegenerative disorders are considered major global health problems associated with nervous system dysfunction, progressive neuronal cell loss with aging, and several pathological and sporadic factors. Parkinson's disease, Alzheimer's disease, Prion disease, Huntington's disease, and multiple sclerosis are the main neurodegenerative diseases that raise significant concern among health scientists. The etiology of different neurodegenerative diseases is different, and they majorly affect the nervous system, including the brain, spinal cord, and peripheral nervous system. Neurodegenerative diseases are linked with motor dysfunction, anxiety, memory loss, depression, cognitive impairments, *etc*. These diseases can be hereditary or caused by toxicity, metabolic disorders, or pathological changes in the brain. Therefore, interest has been growing in the development of different neuroprotective agents of natural origin that could work effectively against these diseases. In that aspect, phytochemicals have shown high potential with minimal side effects in various *in vitro* and *in vivo* studies. Cinnamic acids with phenylpropenoic moiety are abundant in many natural resources. These are available in many forms, such as ferulic acid, caffeic acid, *etc*. They also have a variety of pharmacological properties, including anti-inflammatory, anti-oxidant, anti-amyloid, and neuroprotective properties. This chapter summarizes the role of naturally occurring cinnamic acids and their derivatives to develop the mechanistic aspects of neuroprotective therapeutics in neurodegenerative diseases. Future challenges are also discussed to provide beneficial information and therapeutic strategies.

Keywords: Alzheimer's disease, Cinnamic acid, Huntington disease, Neuroprotection, Parkinson's disease.

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INTRODUCTION

Neurological diseases influence almost 50 million individuals around the world [1]. However, no medications for such diseases are pharmacologically effective for prescribing in these conditions [2, 3]. Aging prompts unfavorable changes in the brain with time, and it is a significantly dangerous factor for several neurological diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD), similar to a stroke. Accordingly, the aging cycle should be studied in order to comprehend the molecular and cellular premise of neurological problems [4, 5]. By the end of 2050, the number of AD patients could reach around 150 million [6]. It has been observed that AD is prevalent in around 0.3% of the population in industrialized countries. This increases with age, rising from 1% of those over 60 to 4% of those over 80. Although the average age of onset is around 60 years, 10% of cases begin at a young age, between 20 and 50. PD is more common in men than in women, with publications citing ratios ranging from 1.1:1 to nearly 3:1 [7]. HD is found worldwide, with a prevalence of around ~12 per 0.1 million among individuals of European descent [8]. The motor symptoms (known as motor onset) can start from a young age in children, and around 45 years in adults, followed by inexorable progression [9].

Neurological diseases can be caused by mutant genetic genes and environmental factors (including sporadic aging and lifestyle). These diseases have standard features like excitotoxicity, reactive oxidative stress (ROS), mitochondrial dysfunctions, synaptic dysfunction, intracellular calcium dysregulation, misfolded protein aggregation, trophic factors, transcription and translation disruptions, axonal transport deficit, and finally, cell loss. Early cognitive and emotional manifestations seen in neurodegenerative disease patients are generally because of the debilitated synaptic and abnormal cellular functions. The disturbed cells that work along with the aging-actuated gathering of damaged DNA and oxidative stress pressure slowly overpower the self-protection framework, including quality control framework (for instance, ubiquitin and autophagy), and others, prompting a change in life, passing equilibrium, and coming full circle in customized cell death or programmed cell death [10]. Many have contended that deficits in brain bioenergetics and metabolism related to aging are fundamental to improving cognitive decline. Mitochondria are essential for energy, and their impairment has been implemented in the aging cycle and positively in neurological disorders [11]. However, little advancement has been made to prevent mitochondrial dysfunctions for improving cognitive brain health [12]. Accordingly, it is important to investigate the changes in mitochondria with aging and disease-associated injury or any other sporadic factors for therapeutic advancement in neurological disorders.

Natural products characterized as small molecular compounds are found naturally in plants, micro-organisms, and animals. These natural products have been utilized for different remedies in different diseases for thousands of years and are demonstrated to be a significant source of new drugs. As per the latest statistics of the US FDA-endorsed drugs, numerous professionally prescribed prescriptions to remedy different diseases are obtained from natural products [13]. Over the years, mitochondrial-targeted natural products have emerged in the discovery of neuroprotective therapeutics. These include possible therapeutics to improve mitochondrial dysfunction, modulate mitochondrial dynamics metabolism, maintain mitochondrial layer potentials, improve mitochondrial bioenergetics, calcium homeostasis, oxidative stress scavenging activities, and anti-inflammatory activities, as well as reduce apoptosis and resolve irregular characteristics in pathological conditions in neurological diseases like AD, PD, HD, multiple sclerosis, and Prion disease [14] (Fig. **1**). It has been observed that cinnamic acid, ferulic, and their derivatives possess numerous biological activities against several neurological diseases Table **1** [14 - 20].

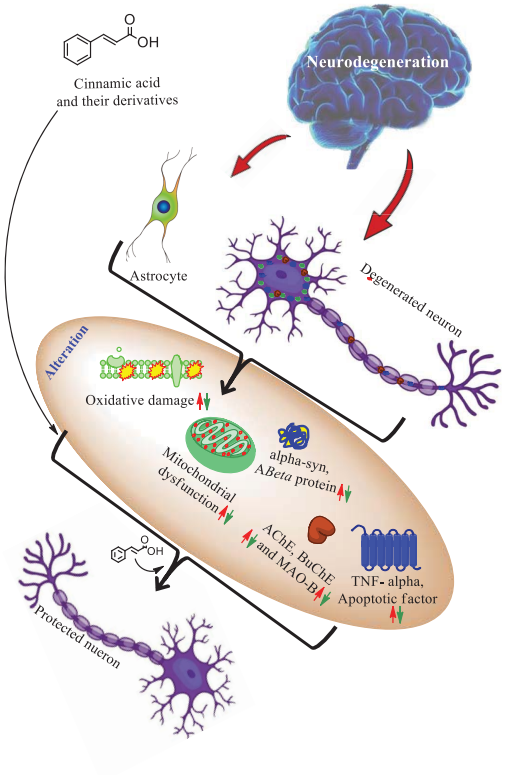

Fig. (1). Cinnamic acid and their derivatives in neuroprotection. α-syn- α-Synuclein, Aβ- Amyloid β protein, AchE- Acetylcholinesterase, BuChE- Butyrylcholinesterase, TNF- α- Tumor necrosis factor-α, effects in neurodegeneration and effects in Cinnamic acid their derivative's neuroprotection.

CHAPTER 4

Phytosome for Targeted Delivery of Natural Compounds: Improving Efficacy, Bioavailability, and Delivery across BBB for the Treatment of Alzheimer's Disease

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Abstract: Alzheimer's disease (AD) is a progressive neurological disorder. Recent studies show that AD is the most common cause of dementia. There are several symptomatic treatments available to counterbalance the neurotransmitter disturbance. Currently, cholinesterase inhibitors are available for the treatment of mild to moderate AD. In addition to that, memantine (an N-methyl-D-aspartate receptor non-competitive antagonist) is also available for moderate to severe AD. Poor blood-brain barrier permeability is a limitation of existing drugs. These drugs may slow the disease progression, but there are chances of reoccurrence of the disease. Several medicinal plants such as *Jasminum sambac, Rosmarinus officinalis, Eucalyptus globulus, Nigella sativa, and Acorus gramineus* are reported to have neuroprotective effects. *Salvia officinalis* has cholinergic binding properties. Ginger root extract may prevent behavioral dysfunction in AD. Extensive research on these plants should be carried out. Drug delivery systems such as lipid nanoparticles, polymer nanoparticles, nano-micelles, nano-gels, liposomes, phytosomes, *etc*., could significantly improve the pharmacokinetics, stability, efficacy and reduce the side effects. Phytosomes have the advantage over other drug delivery systems to selectively target the drugs into the brain. In contrast to traditional approaches, polar phytoconstituents loaded phytosomes

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are more bioavailable on the site of brain tissue, as they can easily go for systemic circulation crossing the Blood-Brain Barrier (BBB). Phytosomes have a low hazard profile as toxicological outcomes are negligible and assure duration of action at a low-risk profile due to upgraded absorption of the active constituents. In addition to this, the improved pharmacodynamic properties of phytosomes make them suitable for the treatment of neurological disorders.

Keywords: Brain cell, Cholinesterase inhibitors, Herbal extract, Liposome, Nano-gels, Phytosomes.

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disorder. It is associated with loss of memory and other cognitive abilities. It is the most common cause of dementia. It accounts for 60-80% of dementia cases. Age is also one of the major causes of AD. There is an increased incidence of AD in people above 65 years of age [1]. In the global scenario, people affected with dementia accounted for about 46.8 million people in 2018, and this figure went up to 50 million in 2020, and the expected prevalence is to be nearly 75 million by 2030. Pathological and biochemical factors also contribute to AD [2]. Cholinergic deficiency is associated with AD. There are very few drugs available for the treatment of AD, though the prevalence of AD is increasing day by day; on the contrary, the treatment modality is limited due to various factors, including the Blood-brain barrier (BBB) [3].

Nature is a good source of medicines. However, written records about medicinal plants date back at least 5,000 years to the Sumerians, who described well-established medicinal uses such plants as laurel, caraway, and thyme [4]. However, due to the high molecular weight of herbal medicines and poor solubility, herbal medicines have less brain permeability. In such a situation, a drug delivery system that can increase the solubility and brain availability of the drugs is desired [5]. Therefore, phytosome based drug delivery systems may be a promising tool for delivering the drugs to the central nervous system [6]. Phyto means part of plants and ‘some’ means lipid mixture. So, herbal drugs embedded in biodegradable lipids are called Phytosomes [7]. Phytosome can be used for improving blood-brain permeability in AD [8]. Considering the above facts, this article aims to summarize the previous findings and latest updates related to phytosomes technology and demonstrate their potential for the development of novel therapeutics in the treatment of AD.

Conventional Therapy Against AD

There are several symptomatic treatments available to counterbalance the neurotransmitter disturbance in AD. Currently, cholinesterase inhibitors such as donepezil, galantamine, and rivastigmine are available for the treatment of mild to moderate AD. They may slow down the disease progression and curb the breakdown of a certain chemical (acetylcholine) in the brain cell. However, these drugs have common side effects like loss of appetite, weight loss, vomiting, nausea, fatigue, diarrhea, and insomnia [9 - 11].

In addition to that, memantine (an N-methyl-D-aspartate receptor non-competitive antagonist) is also available for moderate to severe AD. These treatment options are capable of blocking the disease progression because they may interfere with several pathogenic steps, including inflammation, oxidative damage, iron deregulation, cholesterol metabolism, deposition of extracellular amyloid β plaques, and intracellular neurofibrillary tangle formation [12]. In spite of that, poor blood-brain permeability of existing drug therapy is still a big question because they may delay the disease progression, but there is a chance of reoccurrence of the disease. Again, the limitations of Anti-AD drugs are due to their ineffective action as they reach their target cells in low concentration due to BBB [13]. So, there is a need to find new therapeutic drugs that can effectively counteract neurodegenerative diseases [14].

The new advancement in disease delaying programs includes kinase inhibitors, τ-aggregation inhibitors, and molecules targeting tau protein like modulators of τ-kinases or phosphatases. In addition to amyloid-plaque degradation enhancers and amyloid-β aggregation, inhibitors may also be incorporated in the management of AD [15]. The research progress is on to develop the diagnostic tools that can measure the neuro-biological indications of AD progression. Magnetic resonance imaging (MRI) and blood test (for Plasma Aβ) may improve the accuracy of diagnosis of AD symptoms. Genetic testing is generally not recommended for AD. However, in exceptional cases, family history of people with early-onset AD may be recommended [16 - 18].

Blood Brain Barrier and AD

Recently, only symptomatic treatments exist for all the disease, all treatment aims to counterbalance the neurotransmitter disturbance: cholinesterase inhibitors and memantine. For blocking the progression of the disease, therapeutic agents are supposed to interfere with the pathogenic steps responsible for the clinical symptoms, classically including the deposition of extracellular amyloid β plaques and intracellular neurofibrillary tangle formation. The blood-brain barrier (BBB) protects against circulating toxins and pathogens that could cause brain damage or

CHAPTER 5

Alzheimer's Disease and Physical Activity, Will the Symptoms Improve?

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Abstract: Alzheimer's disease is known to be the most common cause of dementia with increasing number of people suffering every year. In healthy adults, there are millions of neurons in the brain. Degeneration starts and extends in Alzheimer's disease many years before the initial symptoms show up. The neurons taking part in cognitive functions destroy gradually leading to functional disability and finally to death. β-amyloid plaques and tau protein are known as the most responsible causes of Alzheimer's disease resulting in neurodegeneration. Inflammation, atrophy and dysfunction in glucose metabolism will follow. The three stages of the disease include mild, moderate and severe. The patient will have difficulty in cognitive functions, show changes in behavior and will need care for everyday needs, which increases by the disease progress. There are pharmacologic and non-pharmacologic approaches for treatment. The pharmacologic approaches comprise acetylcholinesterase (AChE) inhibitors such as donepezil or N-methyl-d-aspartate (NMDA) receptor blockers like memantine. None of them stops the disease but alleviate the symptoms. On the other hand, non-pharmacologic approaches are usually used to improve the patient's quality of life or improve the behavioral aspects of the disease. Recently, involving physical activity as a non-pharmacologic method of treatment for Alzheimer's disease has been the focus of many studies. This chapter will have a glance at the clinical trials that were conducted regarding the effect of physical exercise and its impact on Alzheimer's disease.

Keywords: Alzheimer's Disease, Dementia, Exercise, Physical Activity.

INTRODUCTION

The first case of Alzheimer's disease was introduced by Dr. Alois Alzheimer in 1907; a 51-year old woman with unusual clinical observations. The first symptom

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was jealousy of her husband, which then progressed to memory loss, disorientation and hallucination. She died four and a half years later. Brain atrophy and arteriosclerotic change in vascular tissues and striking changes of the neurofibrils were reported by Dr. Alzheimer [1]. Histological analysis showed dense bundles of unusual fibrils in nerve cells and senile plaques in the cerebral cortex. The combination of the clinical and histological data came to be known as Alzheimer's disease (AD) [2].

Risk Factors

The most important risk factors for late-onset Alzheimer's disease are age, genetics and family history [3]. The role of older age and its association with Alzheimer's disease remarks the cumulative effects of factors like interactions of genetic susceptibility, biological factors, and environmental exposures [4]. Cardiovascular diseases, brain traumas, depression, diabetes mellitus, increase in LDL, elevation of plasma homocysteine, low skills in occupation or education, lack of intellectual, physical, social and leisure activities, stress and thus elevated plasma cortisone levels are other risk factors for Alzheimer's disease [5, 6].

Pathology

In Alzheimer 's disease, synapses and neurons in the cerebral cortex are lost. The brain shrinks and neurofibrillary tangles (NFT), made up of hyperphosphorylated tau protein are formed inside neurons while amyloid deposits, known as plaques which consist of amino acid peptide (amyloid-beta or Aβ), are present outside neurons. The neurons die and the brain tissue is damaged. Alzheimer's disease slowly progresses. Many years before the symptoms show up, the disease has already begun [3, 4, 7].

Pharmacologic Treatment of Alzheimer's Disease

The currently used pharmacologic medications for Alzheimer's disease do not slow the progress or stop the destruction of neurons; they just alleviate the symptoms. There are two accepted categories of treatment that modulate the neurotransmitters in the brain, cholinesterase inhibitors and N- methyl- D-aspartate (NMDA) receptor antagonists [3, 8].

Cholinesterase Inhibitors

Cholinergic neurons are selectively reduced in Alzheimer's disease (AD). To overcome the situation, anti-cholinesterases, precursors of acetylcholine and cholinomimetics have been used for the treatment of AD with anticholinesterases being the most successful among them. Tacrine, donepezil, and galantamine reversibly inhibit acetylcholinesterase while rivastigmine is a reversible inhibitor of both acetylcholinesterase and butyrylcholinesterase. These enzyme inhibitors

prevent the breakdown of acetylcholine at the synapses of cholinergic neurons [4, 6, 8]. It should be noted that tacrine elevates the levels of serum aminotransferase and might induce liver toxicity [9].

N-methyl-D-aspartate (NMDA) Receptor Antagonists

Memantine belongs to this category and is able to block glutamate at its sites of action and protect neurons by improving synaptic transmission and/or preventing calcium release [6, 8].

Should Non-Pharmacologic Treatments Be Involved?

The most prevalent cause of dementia in older people is Alzheimer's disease making up 60-80% of all dementias. One in eight of adults over 65 are struggling twith AD; yet, there are no solution for prevention or overcoming the disease [10].

Alzheimer's disease gradually results in cognitive deterioration, functional decrementation, dependency and reduced quality of life [11, 12]. Disabilities in patients with Alzheimer's disease force them to be dependent on their caregivers. Stiffness, weakness in muscles and more risk of falling are other points of concern [13]. Balance performance is disturbed in older people and thus they are more susceptible to fall, a situation worsened in dementia [14].

To support brain health in older people, both pharmacologic and non-pharmacologic treatments have been the focus of researchers (Fig. **1**) . Clinical trials conducted in the recent two decades have tried to aim the pathological features, but other mechanisms also need to be considered [15, 16]. The available pharmacologic treatments just decelerate the symptoms, not stop them [17, 18] and may also cause unwanted effects such as gastrointestinal problems and insomnia. On the other hand, non-pharmacologic treatments can be used as alternatives or supplements [19].

Recently, there has been interest for research about non-pharmacologic treatments of Alzheimer's disease. Studies have shown that being involved in mental or physical activities will reduce the occurrence of dementia [18]. Some non-pharmacologic interventions for alleviating the behavioral symptoms of AD include educating the caregivers, managing the environment, psychotherapy, cognitive treatment, physical trainings, and occupational therapy [18, 20]. These interventions have positive effects on activities of daily living in AD patients [11, 21, 22].

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Dr. Amtul, due to her background in clinical psychiatry and neurodegenerative disorders, brings expertise in neuroanatomy, pathophysiology, drug development, and diagnosis of brain disorders. Dr. Amtul's main area of research has been chemical biology and medicinal bioinorganic chemistry. Dr. Amtul has extensively researched the biochemical, molecular, and behavioral substrates of memory impairment in Alzheimer's disease, vascular cognitive impairment, stroke, depression, epilepsy, and frontotemporal dementia-related disorders using biochemistry, structural biology, optogenetics, decoy, and Trojan horse technologies, bioinformatics, and computational biology. Dr. Amtul is a recipient of several national and international awards in basic and SoTL research, including J. William Fulbright Award from the USA, the Alexander von Humboldt-Stiftung Award from Germany, Ontario Mental Health Foundation, and the CIHR Strategic Training Awards from Canada, as well as a few International Traveling grants.