Frontiers in Clinical Drug Research

(CNS and Neurological Disorders)

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Frontiers in Clinical Drug Research - CNS and Neurological Disorders

(Volume 7)

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PREFACE

The Central Nervous System is undeniably one of the most complex systems of the body. Neuroscientists all over the world are busy exploring this fascinating mystery of the biological system. There has been a tremendous increase in our knowledge about the brain, spinal cord, and peripheral system during the last couple of decades. Yet we still learn something new every day about the multifold obscurities of the nervous system.

The present book is an effort to inform our readers with the new milestones being explored and uncovered every day in the field of neuroscience. The six chapters cover state of the art cutting-edge contributions from eminent leaders in the field. Chapter 1 covers the role of fatty acid amides as new potential therapeutic agents to treat multiple sclerosis; chapter 2 highlights the use of machine learning techniques to detect epileptic seizures; chapter 3 outlines the present and future directions about the essential tremor neurodegeneration in essential tremor; chapter 4 presents the potential therapeutic role of the melatoninergic system to treat epilepsy and comorbid depression; chapter 5 evaluates how the transgenic model of drosophila is being used to model neurodegenerative diseases, and chapter 6 summarizes the importance of genetic basis in stroke as the potential drug target. In brief, each chapter covers a wide-ranging, analytically evaluated body of work such as pathogenesis, therapeutic evidence, targets, and mechanisms of action of therapeutics to treat brain disorders in a very compelling way.

I believe that this book will be of considerable interest for both experienced scientists from the neuroscience community as well as for beginners in the field.

I am grateful for the timely efforts made by the editorial personnel, especially Mr. Mahmood Alam (Director Publications), and Mrs. Salma Sarfaraz (Senior Manager Publications) at Bentham Science Publishers.

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CHAPTER 1

Fatty Acid Amides as a New Potential Therapeutic Agent in Multiple Sclerosis

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Abstract: Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS) frequently starting in young adulthood. However, the pathogenesis of the progressive disease phase is still not well-understood, and the inflammation as well as the mechanisms of demyelination and tissue damage is currently being discussed. The available drugs approved in the treatment of different clinical forms of MS prevent the relapses, alleviate the symptoms only partially and slow progression of the disease; however, none of these treatments is capable in stopping the MS clinical course. Moreover, approved MS treatments lead to unpredictable adverse effects associated with a range from mild (such as flu-like symptoms, fatigue, liver transaminase elevation, stomach pain or irritation at an injection site) to serious (such as bradycardia or progressive multifocal leukoencephalopathy). It is time to revise the MS drug development strategy by relying on our endogenous defense mechanisms. Endogenous fatty acid amides (FAAs) are a family of structurally different molecules found in mammalian systems. These compounds include anandamide, oleoylethanolamide and palmitoylethanolamide; research preclinical and clinical reported anti-inflammatory and neuroprotective activity of FAAs making them an alternative therapeutic approach in neurological disorders. In consideration that an endogenous compound able in the control of endogenous defense mechanisms can assume extraordinary importance, this chapter includes a discussion on current approved drugs in MS, and on pharmacological properties of FAAs that may play a promising role in complementing of medication approved for use in MS.

Keywords: Autoimmune disease, Anandamide, Cortical lesions, Endogenous mechanisms, Experimental autoimmune encephalomyelitis, Grey matter, Immune regulatory molecules oleoylethanolamide, Multiple sclerosis, Neuroinflammation, Pain, Palmitoylethanolamide, Preclinical studies, White matter.

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INTRODUCTION

Patients living with multiple sclerosis (MS) experience symptoms that negatively affect their quality of life (QOL) when the central nervous system (CNS) disease disrupts nerve signal transmission. It is crucial to supply those who suffer from these symptoms with therapeutic treatments that facilitate healing. Due to the complexity and disease burden of MS, a multidisciplinary management approach that combines pharmacologic and integrative non-pharmacologic therapies is urgently required to provide patients with rapid and effective care.

MEDICAL OVERVIEW OF MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is an inflammatory, autoimmune, demyelinating disease of the central nervous system (CNS) characterized by focal lesions (called plaques) disseminated within of multiple CNS regions. Magnetic resonance imaging (MRI) can accurately detect the demyelinating lesions in white matter (WM), which can be used to provide the clinical diagnosis. The concept that MS is an inflammatory demyelinating disease of WM was established about 50 years ago; recent advances in immunohistochemical staining and MRI sequences have allowed establishing that the focal demyelinating plaques can also damage the grey matter (GM) [1]. Although the MS onset usually occurs in young adults between 20-45 years of age [2], recent clinical studies report MS diagnosis in children and adolescents [3]. MS typically affects young adults, with an initial demyelinating event between 20 years and 40 years of age [3] and has a higher prevalence in women, although it has estimated that more than 10% of persons affected have a history of MS signs or symptoms onset before age 18 [4]. The relapsing-remitting (RR) is the most common clinical form of MS characterized by new attacks (relapses or exacerbations) or a worsening of pre-existing neurologic symptoms associated with a damage of CNS area, followed by periods of partial or complete recovery (remissions). Following this clinical phase, more than half of RR-MS patients switch into a secondary-progressive clinical form of MS (SP-MS), characterized by a worsening of neurological functions (accumulation of disability) independent of acute attack [5]. SP-MS form is characterized by either active phase (with relapses and/or new contrast-enhancing lesion captured by MRI) or not active phase, as well as clinical progression (evidence of disease worsening on an objective measure of change over time, with or without relapses) or without clinical progression. MS patients (approximately 10%) can also experience a disease course characterized by worsening neurologic functions (accumulation of disability) from the onset of symptoms without early relapses or remissions; this clinical condition is defined as primary progressive of MS (PP-MS). Patients affected by progressive MS clinical forms may also exhibit occasional relapses; this subtype of clinical form is classified as progressive-

relapsing MS (PR-MS), whereby relapse occurs alongside progression of the disease. Actually, it is still unknown whether MS has a single or multiple causes; nevertheless, factors genetic [6], exposure to virus [7], low exposure to vitamin D [8] may be among the potential causes of MS-related disease activity. Emerging evidence through experimental autoimmune encephamomyelitis (EAE) model, the most commonly used experimental model of MS, has revealed that components of the intestinal microbiome may be involved in autoimmune response, and along this line evidence for a similar cause is beginning to emerge in MS patients [9]. The scientific community is aware that actually non-curative treatment can stop the disease activity as well as the progression of MS. Although, as on December 2017 the Food and Drug Administration (FDA) has approved 15 disease-modifying treatments (DMTs), these medications attenuate the severity of relapse-related effects, and slow but not stop the disability progression. In addition, with the increasing number of medications approved by the FDA, has also increased the risk and the severity of side effects during the treatment. Therefore, the research of new medications capable to rest or slow the MS progression with minimal side effect is becoming increasingly necessary. The current knowledge about the endogenous role of fatty acid amides (FAAs) is taking into consideration the potentiality and effectiveness of this class of neuromodulatory lipids including endogenous cannabinoid N-arachidonoyl ethanolamine (anandamide; AEA), N-palmitoylethanolamine (PEA) and N-oleoylethanolamine (OEA) as therapeutic agents. This chapter highlights the preclinical and clinical outcomes of FAAs making them a promising complementary therapy to the medications currently approved for the treatment of MS-related symptoms.

PATHOGENESIS OF MULTIPLE SCLEROSIS

Actually the exact pathogenesis of MS is still unknown; however the demyelination event is characterized by a lymphocytic (mainly T helper cells) infiltration from periphery to CNS, microglia activation to demyelination and axonal degeneration [10]. Once into the CNS, T- lymphocytes can be reactivated by local professional antigen presenting cells (APCs) like macrophages, microglia and dendritic cells, which are present in human and mouse CNS lesions [11 - 13]. The lymphocytic presence within lesions and bordering areas suggests that inflammatory destruction in MS is driven not only by antigen-specific targeting of myelin, but also by other CNS components like oligodendrocytes, axons, nerve cells and astrocytes [12]. How T-cells become abnormally activated toward CNS antigens remains unclear. In addition to T cells, B cells and their products are involved in the pathogenesis of MS; indeed, it has long been recognized that B cells differentiate into plasma cells to produce antibody molecules closely modeled after the receptors of the precursor B cell. Once released into the blood

CHAPTER 2

Epileptic Seizures Detection Based on Non-linear Characteristics Coupled with Machine Learning Techniques

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Abstract: The use of transformation techniques (such as a wavelet transform, Fourier transform, or hybrid transform) to detect epileptic seizures by means of EEG signals is not adequate because these signals have a nonstationary and nonlinear nature. This paper reports on the design of a novel technique based, instead, on the domain of graphs. The dimensionality of each single EEG channel is reduced using a segmentation technique, and each EEG channel is then mapped onto an undirected weighted graph. A set of structural and topological graph characteristics is extracted and investigated, and several machine learning techniques are utilized to categorize the graph's attributes. The results demonstrate that the use of graphs improves the quality of epileptic seizure detection. The proposed method can identify EEG abnormities that are difficult to detect accurately using other transformation techniques, especially when dealing with EEG big data.

Keywords: Epileptic EEG Signals, Graphs, Modularity, Multi-Channel, Statistical Features.

INTRODUCTION

Epilepsy is a chronic neurologic disorder characterized by recurrent unprovoked seizures. The disorder affects more than 40 million people around the world, most of them young children and older adults. Developing countries contribute around 85% of those epilepsy cases. Several clinical studies have shown that epilepsy can

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be caused by interactions between several genes and environmental factors. However, people who have suffered brain damage, strokes, toxicity, and high fever could be prone to epileptic seizures. During an epileptic seizure, the brain neurons discharge suddenly, and abnormal activities occur within the cerebral cortex.

A seizure usually lasts about two minutes or less, depending on the age of the patient and the health of the brain [1]. Epileptic seizures can be controlled by medications and, in some severe cases, surgery could be a solution. To diagnose epilepsy, an electroencephalogram (EEG) as a means of recording the electrical activity of the brain and how brain neurons are functioning can detect abnormalities in brain activity.

Much research has been done based on using EEG signals to identify and trace the abnormities produced by epileptic seizures. Many of these studies have been conducted based on wavelet and Fourier transformations [2 - 5]. For example, Kumar *et al*. [4] analysed epileptic seizures by adopting a wavelet transformation based on an approximate entropy. An EEG signal was decomposed into five levels. Then, the approximate entropy was calculated as a representative feature. Two machine learning algorithms—a support vector machine (SVM) and a neural network—then were utilised to classify EEG features into epileptic and non-epileptic segments. Orosco *et al*. [5] employed a stationary wavelet transform to extract EEG features. Several spectral features were extracted and investigated using a stepwise approach to identify the most effective feature set for detecting epileptic seizures. In another study, Bajaj and Pachori [1] applied an empirical mode decomposition to study the behaviour of EEG signals during epileptic seizures: the characteristics of bandwidth were used to classify EEG signals into epileptic and non-epileptic using an SVM. Moreover, Hassan *et al*. [3], in considering 6 spectral features, showed that a tunable-Q factor wavelet transform (TQWT) with a bagging technique was a good tool for detecting epileptic seizures. A combination of several machine learning algorithms was integrated as an ensemble classifier. Guler *et al*. [2] studied wavelet coefficients with the Lyapunov exponent to analyse EEG signals: in this case, an SVM classifier was utilised to differentiate EEG groups. All the above-mentioned research was conducted using the Bonn University data (described below) that is used in our study.

More recently, Gao *et al*. [6] suggested a recurrence time-based approach to detect epileptic EEG signals. In that study, EEG signals were segmented into overlap and non-overlap intervals. Three EEG channels were involved to record epileptic EEG signals. Another study was conducted by Gao *et al*. [7], in which a nonlinear adaptive multiscale decomposition approach was proposed to analyse

nonstationary signals. Epileptic EEG signals were taken as an example in that study. Gao *et al*. [8] also studied epileptic EEG signals using several complex measures. Amin *et al*. [9] utilised a wavelet transform to decompose EEG signals into approximations and detail coefficients. In that study, an arithmetic coding model was used to convert wavelet coefficients into bitstreams. San-Segundo *et al*. [10] suggested a deep neural network model to detect seizures in EEG signals. In that study, they employed two convolutional layers for the feature extraction and three layers for the classification. Wang *et al*. [11] applied Fourier transform to analyse EEG signals. A set of features was extracted and reduced using a principal component analysis. A random forest model coupled with a grid search optimization was utilised to classify the extracted features.

This paper describes an approach that addresses the detection of epileptic seizures in EEG signals in a way that differs from that of preceding studies. In this study, the dimensionality in EEG signal data is reduced to extract relevant information before mapping it to graphs, simultaneously eliminating data that is redundant. The statistical characteristics of EEG signals are extracted through a segmentation technique. Based on our previous work, using statistical characteristics of EEG signals in constructing graphs could contribute to improving the ability of the graphs to reflect any abnormal behaviours in EEG signals [12]. In this method, after a thorough investigation, we segment each single-channel EEG signal into four windows of 1024, 1024, 1024, and 1025; then, each segment is split further into 32 clusters. Eight statistical characteristics are extracted from each cluster, and a vector of statistical features is then mapped into an undirected graph. To detect the abnormal patterns of epileptic seizures in EEG signals, Jaccard coefficients, degree distribution, modularity, entropy, high degree, low degree, and other local and global graph characteristics are extracted and analysed. Different machine learning techniques, including least support vector machine (LS-SVM), Naïve Payson (NB), k-means, and k-nearest, are used to categorize network characteristics into different EEG cases. The main objective of this method is to improve the detection accuracy of epileptic seizures in EEG signals by integrating the graph concept with a statistical model, thus determining the best graph feature set for analysing epileptic EEG signals.

EEG DATA

The epileptic EEG datasets used in this research are available online from http://epileptologie -bonn.de/ cms/front_content.php?idcat=193 &lang=3. The datasets are considered a clinical EEG benchmark database for most epileptic research. Further details of the datasets are described [13].

CHAPTER 3

Hampering Essential Tremor Neurodegeneration in Essential Tremor: Present and Future Directions

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Abstract: Essential tremor (ET) is one of the most prevalent neurological disorders worldwide. ET presents mainly with kinetic and action tremor in upper limbs. Tremor may also affect the head and some patients develop an ataxic gait, as well as cognitive/affective symptoms. ET significantly impacts the quality of life. There is accumulating evidence that ET is a slowly progressive neurodegenerative disease, driven by both genetic and environmental (possibly dietary) factors. Both the olivo-cerebellar pathways and the cerebellar cortex are critically involved, with particular impairments in the morphology of the Purkinje neurons (Purkinjopathy) as well as the surrounding micro-circuitry. Dysfunctional cerebello-thalamo-cortical loops probably result in bursts of tremor. So far, only few symptomatic medications are available, including beta-blockers, primidone and drugs aiming to modulate GABAergic transmission such as topiramate or gabapentine. Surgery (deep brain stimulation, thalamotomy) is proposed to refractory cases but carries the risk of infection, bleeding in the brain and several technical issues related to the mispositioning of electrodes. MRI-guided focused ultrasound is a promising technique, but long-term follow-up is missing. Repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) are encouraging non-invasive techniques but no consensus on optimal protocols has been reached so far. It is remarkable to observe that none of the available therapies targets the neurodegenerative process affecting in particular the cerebellum, the masterpiece of progression of the disease. This chapter focuses on the pathogenesis of ET and discusses possible novel avenues for therapy and prevention. In particular, the impact of environmental toxins such as beta-carboline alkaloids (βCAs), possibly generated from Maillard-type reaction products, is discussed. Animal models of ET, toxicokinetics and neurotoxic effects of βCAs are presented, with an emphasis on the neuroprotective pathways that are candidates to block the neurodegenerative process. Moreover, we consider a group of enzymes that could be neuroprotective, especially GAD65 and GAD67, involved in GABA synthesis/neurotransmission, and MAO_A/MAO_B. Finally, we emphasize the potential interest of dietary phytochemicals

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(such as phenolic acids, catechins, flavonoids, anthocyans, stilbenoids, curcuminoids) and herbal therapies (based *i.e.* on *Bacopa monnieri, Ginkgo biloba*) as neuroprotective approaches to hamper the neurodegenerative process in ET.

Keywords: β-Carboline Alkaloids, Chemoprevention, CNS Disorder, Deep Brain Stimulation of the Thalamus, Essential Tremor (ET), ET Pharmacotherapy, ET Animal Model, (GABA)ergic Dysfunction, Gamma Knife Surgery (GK), Harmane, Harmaline, Maillard Reaction, Neuroprotection, Neurodegenerative, Neurotoxicity, Purkinje Neurons, Repetitive Transcranial Magnetic Stimulation (rTMS), Thalamotomy.

ESSENTIAL TREMOR: DEFINITION AND EPIDEMIOLOGY

Essential tremor (ET) is characterized by a slowly progressive postural and/or kinetic involuntary tremor, a bilateral action tremor affecting predominantly the arms, the head and/or the voice [1]. ET is primarily a kinetic tremor; the main clinical features of ET consist in kinetic tremor of the arms (tremor occurring during guided voluntary movements) with frequencies of 4 to 12 Hz, followed by postural and/or kinetic tremor of cranial structures (*i.e.* neck, jaw, voice) [2]. Patients usually first become aware of the tremor when they are holding newspaper or utensils or when reaching for objects. When ET affects the neck muscles, patients exhibit either yes-yes or no-no oscillations of the head. Furthermore, ET can affect the vocal cords, causing a tremulous voice while singing or talking [3]. As time evolves, ET tends to impair balance and gait, and may even cause falls.

Apart from the first group of motor features, recent research points out a variety of cognitive and psychiatric signs. One of the most common non-motor symptoms in ET is the presence of mild cognitive deficits [4], notably for verbal fluency, naming, mental set-shifting, verbal memory, and working memory; deficits in olfaction and hearing loss have also been observed in ET but the published studies remain inconclusive [5]. Significant relationships are reported between ET and depression [5], poor nocturnal sleep quality and sleep disturbances [6]. Non-motor symptoms could be a part of the disease in the early stages; indeed depression and anxiety are more common in young patients with ET [6]. In fact, depressive symptoms appear to be stronger predictors of tremor-lowered quality of life than the motor aspects of tremor itself [7].

Obviously, and even if some patients will never come to medical attention, both motor and non-motor ET symptoms result in significant psychosocial and physical disabilities, interfering with activities of daily living (ADL) such as eating, drinking, writing [3]. The classical view of ET as a monosymptomatic

condition is now replaced by the concept of a heterogeneous disorder with multiple motor and non-motor features of varying degrees.

Incidence and Prevalence

ET is among the most prevalent disabling and poorly understood neurological movement disorders, especially affecting elderly people, but also appearing in young adults and even during childhood [8]. The disease has been reported not only by neurologists, but also by internists, geriatricians, and general practitioners [9]. The adjusted incidence is about 619 per 100.000 person-years among persons aged 65 and older [10]. However, the prevalence estimates have varied enormously amongst studies and it is therefore difficult to establish the prevalence at a world level. A meta-analysis by Louis and Ferreira identified 28 studies over 19 countries, with prevalence ranging from 0.01% (Nigeria, China; all ages) to 20.5% (USA; over 65 years) (Fig. **1**). By pooling prevalence in all age classes, the

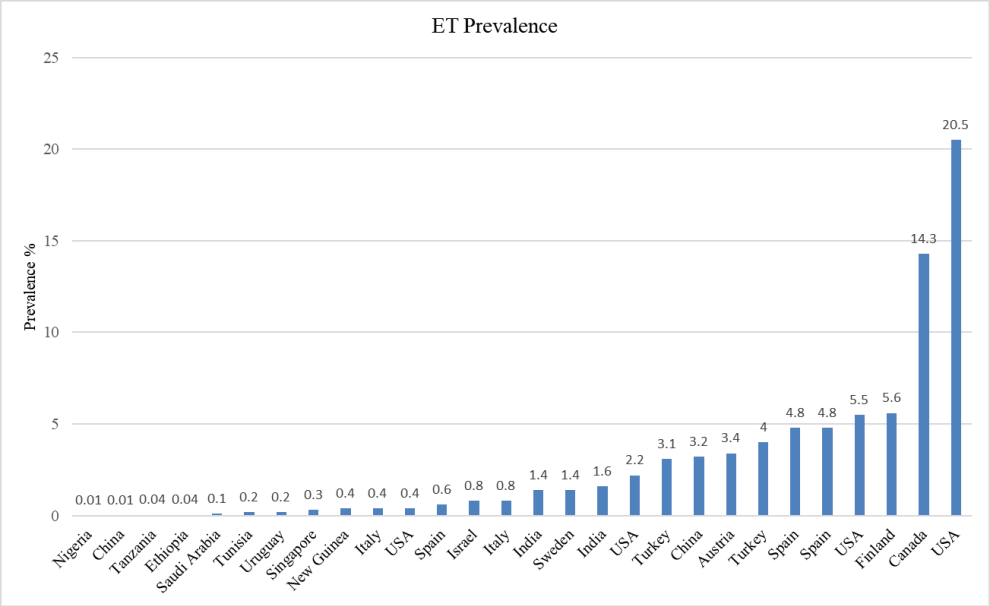

Fig. (1). Studies are ordered from lowest to highest prevalence (expressed in %). There are differences between studies regarding the screening process and epidemiological methods, in addition of variability in terms of age of examined subjects (notably, Canadian and US studies gather mainly patients in the elderly) [Adapted from [11]].

worldwide prevalence was then estimated at 0.9%. The prevalence markedly increased with age (4.6% for age ≥ 65 years), and especially with advanced age.

CHAPTER 4

The Potential Therapeutic Role of the Melatoninergic System in Treatment of Epilepsy and Comorbid Depression

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Abstract: Pharmacoresistant epilepsy is estimated to affect about 30% of patients with epilepsy and predisposes to a higher risk for psychiatric comorbidities and depression. This is one of the most common complications in epilepsy but the mechanisms underlying its development are still unclear. Periclinical studies have shown that selective serotonin reuptake inhibitors (SSRIs) are ineffective against comorbid depression. Dysfunction in circadian rhythms which are driven by the suprachiasmatic nucleus (SCN), is a hallmark of depression. The activity of this circadian pacemaker is under the fine-tuning control of the endogenous hormone melatonin. Over the past decade, there has been extensive research on the therapeutic potential of melatonin and its analogues in the management of both epilepsy and depressive disorders. Melatonin and its analogues targeting the melatonin MT_1 and MT_2 receptors are considered as potential adjuvants for the treatment of epilepsy associated with moderate-to-strong antioxidant, anti-inflammatory, and neuroprotective activity at non-toxic doses. One of the main advantages of the melatonin system is associated with its chronobiotic properties and pivotal role in the resynchronization of disturbed circadian rhythms of different parameters. This chapter summarizes the available experimental and clinical data on melatonin and drugs acting on the MT receptors, which are currently of therapeutic interest in the treatment of epilepsy and depression. Despite the fact that melatonin and drugs based on MT receptors have been used for many purposes over the last three decades, the available data on the potential implementation of melatonin compounds in epilepsy and comorbid depression are scarce. The many unanswered questions regarding the use of melatonin to treat epileptic seizures and complications associated with epilepsy are briefly summarized.

Keywords: Epilepsy, Comorbid depression, Circadian rhythms, Melatonin, Antioxidant, Anti-inflammatory, Neuroprotection, Chronobiotic properties, Treatment.

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INRODUCTION

Epilepsy is the fourth most frequent neurological condition and is characterized by recurrent seizures. During seizure onset a pathological and hypersynchronous discharge of clusters of neurons takes place in the brain causing involuntary movements, disturbed emotional and sensational state and, occasionally, loss of awareness. Epileptic patients often suffer of psychiatric complications, especially depression, which represents one of the most common comorbidities leading to worsened quality of life [1, 2]. Several reports considering the link between seizures and depressive behavior suggest a lack of dependence of the comorbid psychiatric state on seizure severity and frequency [3, 4]. Epilepsy has been examined as a risk factor for the appearance of comorbid depression and vice versa thereby confirming the hypothesis that epilepsy and depression have a common underlying pathophysiology [2, 5 - 8]. However, the question about the causal relationship between the two conditions, *i.e*. whether epilepsy leads to depression or vice versa, is still open. Studies exploring comorbid depression reveal that most of the cases in epilepsy patients are atypical or referred to as interictal dysphoric disorder [9 - 12]. For the elaboration of future successful therapies, it is important to understand the underlying mechanisms of comorbid depression in epilepsy which might be different from those of functional depression. Among epilepsy patients, those with temporal lobe epilepsy (TLE) are most frequently diagnosed with comorbid depression. Therefore, TLE models are the most appropriate for exploration of the underlying structural and functional links between the two conditions. In this regard, there is evidence from magnetic resonance imaging that TLE and depression are associated with: 1) common neuronal circuits and connecting pathways, including the temporal, entorhinal, neocortical and frontal lobes with the cingulate gyrus, hippocampus and amygdala, as well as the basal ganglia and thalamus; 2) smaller total brain volumes and/or thinner cortical mantle; 3) hyperactive hypothalamic–pituitary–adrenal (HPA) axis; 4) down-regulated serotonin $(5\text{-HT})_{1A}$ receptors in the mesial frontal, temporal and insular regions, as well as in the raphe nuclei; 5) inflammation (high plasma levels of pro-inflammatory cytokines and gliosis in brain) 6) disrupted balance between excitatory and inhibitory systems [13 - 15].

The majority of currently used anti-epileptic drugs (AEDs) target classical inhibitory GABAergic (*e.g.* phenobarbital, benzodiazepines) and excitatory glutamatergic (Glu) (perampanel) neurotransmitter systems, voltage-gated Na^+-(phenytoin, carbamazepine), or voltage-gated Ca^{2+}-channels (ethosuximide and gabapentin). The necessity to control seizures in severe forms of epilepsy requires high-dosage mono- or polytherapy that is often accompanied by serious side effects, including depression [16]. So far, efficient drugs with disease-modifying capacity which are able to prevent the development of comorbid psychopathology

in chronic epilepsy, including depressive state, are lacking on the market. Therefore, understanding the underlying mechanisms either through appropriate animal models or on the basis of clinical data with functional imaging is crucial for the identification and characterization of new effective therapies. In this regard, a substantial amount of information to assist the development of new AEDs, which would be beneficial for complications associated with epilepsy, including comorbid depression, can be obtained from adequate animal models of epilepsy with comorbid depression. The results from such studies would lead to the promotion of promising compounds.

Animal models of TLE associated with depression have already been elaborated by several laboratories [17 - 24]. In different models of epilepsy, animals have demonstrated despair-like behavior in the forced swim test (FST) and anhedonia in a test for preference to sucrose solution (SPT), along with hyperactivity of the HPA axis, inflammation in specific brain structures and in the periphery, structural alterations (atrophy of limbic structures) and functional abnormalities (abnormal theta activity). An intrinsic approach is necessary to explore how early anticonvulsant and antidepressant treatment, even prior to the onset of seizures, will affect the development of epileptogenesis and its concomitant behavioral psychiatric outcome.

The present chapter is focused on preclinical and clinical findings considering the role of the melatonin system in epilepsy and depression, respectively. It also discusses the perspectives for research directed towards the beneficial use of this system against the development of comorbid depression in epilepsy.

PATHOGENESIS OF EPILEPSY

Most epilepsies are caused by brain trauma and are acquired after a latent period of epileptogenesis characterized by neuroplastic reorganization. The general mechanism causing all forms of epilepsy involves an impaired balance between excitatory and inhibitory neurotransmission with dominant excitation. Normally, excitation is under the tonic control of inhibitory interneurons. Different factors such as trauma, genetic mutation, brain tumor, or a number of other complications may result in focal hyperexcitability, which can propagate throughout the central nervous system (CNS) and disrupt the regulatory inhibitory mechanism maintaining a fine-tuning control.

The excitatory/inhibitory equilibrium of the CNS is under the precise control of different modulators and co-transmitters that can affect GABA and Glu neurotransmission through signal transduction [25]. The primary clinical hallmarks in epilepsy are seizures. Mitochondrial dysfunction, oxidative stress,

CHAPTER 5

Modeling Neurodegenerative Diseases Using Transgenic Model of *Drosophila*

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Abstract: From the past several decades, neuroscientists have been focusing on understanding the mechanisms of various human neurodegenerative diseases using different models such as *Mouse*, *Rat*, *Zebrafish*, *worm* and *the Drosophila*. Among them, the *Drosophila,* with a short generation time and genetic amenity, has emerged as a vital and prevailing model system to explore multiple aspects of neurodegenerative diseases like Alzheimer's disease, Parkinson's disease, Huntington's disease, Amyotrophic lateral sclerosis, *etc*. In this chapter, we have presented various molecular, genetic and therapeutic approaches employed to model human neurodegenerative diseases using *Drosophila.* Furthermore, we also present the worldwide prevalence of neurodegenerative diseases, along with a survey of published literatures of research conducted in the last two decades on major neurodegenerative diseases employing transgenic *Drosophila,* to evaluate where we stand.

Keywords: Neurodegeneration, Senile plaques, Neurofibrillary tangles, α-Synuclein, Huntingtin, CAG repeat, MARCM system, GAL4 /UAS binary system, CRISPR-Cas system, Therapeutics.

INTRODUCTION

Neurodegenerative disease refers to the gradual loss of neurons of central nervous system (CNS) and peripheral nervous system (PNS) leading to structural and functional damages. The CNS includes brain and spinal cord which control most functions of the body and mind, while PNS includes cranial nerves, peripheral nerves, nerve roots, and neuromuscular junctions positioned outside the brain and spinal cord [1]. Most common neurodegenerative diseases are Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), Frontotem-

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poral dementia (FTD), Spinocerebellar ataxia (SCA), Multiple sclerosis (MS), and Amyotrophic lateral sclerosis (ALS) [2]. The symptoms of neurodegeneration also manifest in certain other conditions like neuroinfections (due to bacteria and viruses), head trauma, stroke, brain tumors *etc.* [1]. Here, we are focusing on four most prevalent neurodegenerative diseases *i.e.*, AD, PD, HD, and ALS which are quite straight forward for modeling in fruit flies.

In Alzheimer's disease (AD), primarily two candidates, Amyloid-β and Hyper-phosphorylated Tau proteins have been implicated. Over expression/ mutation of the concerned genes lead to neuronal cell death and progressive loss of memory. The amyloidogenic mode of enzymatic action on Amyloid precursor protein (APP) results in Amyloid aggregates over a period of time to form Amyloid plaques. Although, normal function of Amyloid-β is not well understood, plaques evoke numerous neurotoxic effects. On the other hand, hyper-phosphorylated Tau protein leads to formation of neurofibrillary tangles (NFTs). Tau protein is also implicated in the progression of Parkinson's disease, suggesting the susceptibility of AD patients to develop PD symptoms [3]. Several lines of research also indicates greater chances of developing AD like symptom in PD patients and *vice versa* [4, 5]. This might be due to the presence of the common culprit, reactive oxygen species (ROS)/ reactive nitrogen species (RNS), which act as linking agents for neurodegenerative diseases including AD, PD, and HD [6].

Parkinson's disease (PD) is the most common movement disorder. The major proteins involved in PD progression include SNCA (OMIM 163890), Parkin/PARK2 (OMIM 602544), DJ-1 (OMIM 602533) and LRRK2 (OMIM 609007). Mutation and/or misregulation of the genes concerned with these proteins cause neuronal cell death, importantly dopaminergic neurons loss, which ultimately hampers the secretion of dopamine [17].

Huntington's disease (HD), which falls under Polyglutamine (PolyQ) disease group, is a hereditary disease, characterized by progressive loss of brain cells, mainly in ganglion region, and exhibits destruction of mental ability. Previous studies reported that alteration in dopamine (DA) neurotransmission was found in HD patients and also in genetic mouse models of the disease [7, 8]. The modulation in DA transmission level affects the behavioral flexibility and leads to increased risk of Huntington disease [7, 8]. The key protein involved in HD is Huntingtin protein encoded by *HTT* (OMIM 613004) gene. Mutations in this gene lead to growing CAG repeats translated into a PolyQ stretch. The increasing PolyQ stretches manifest in the form of enhancement of motor neuron degeneration. A report revealed that a fifty eight year old male suffering with HD was diagnosed with a coexistence of motor neuron complication, which is an indication of Amyotrophic lateral sclerosis [9].

In ALS, the motor neurons lacking neuronal muscle nourishment cause atrophy or progressive loss of motor neurons affecting the daily work schedule [10]. There are mainly two form of ALS, sporadic and familial. Sporadic ALS is more common and is caused without a clear reason known, accounts upto 90-95% of the cases, while familial ALS shows genetic inheritance and accounts for approximately 5-10% of the cases. However, mutations in genes such as *CHCHD10, TBK1, NEK1, C9orf72* and *SOD1*, enhances the possibility of ALS [11, 12]; In America, familial ALS cases are more prominent due to mutation in genes *c9orf72* (*chromosome 9 open reading frame 72*) and *SOD1 (superoxide dismutase*) [13]. Several reports revealed that mutation in *SOD1* gene causes deposition of misfolded SOD1 proteins in motor neuron. Aggregation of SOD1 proteins, responsible for the mitochondrial dysfunction, ultimately disturb the ATP homeostasis [14]. Therefore, previous studies have been suggesting that these diseases are linked with each other directly or indirectly and often increase the risks of neurodegeneration. Here, we discuss genome wide gene expression studies that link between the neurodegenerative diseases through more genes at a systems wide network level such as, a microglia enriched gene co-expression network is a common link that underlies AD, HD and PD [15]. In past decades, transgenic *Drosophila* has been widely used to understand the molecular aspects of these neurodegenerative-disease progressions, especially, since it offers a simple system for a large scale drug screening.

This book chapter also highlights the key proteins that play an important role in neurodegeneration and the brain regions they affect (Table **1**).

Table 1. Key proteins involved in human-neurodegenerative diseases and the affected brain regions.

S.No.	Disease name	Key proteins	Affected human brain region
1	Alzheimer's disease (AD)	Amyloid-β, Tau	Hippocampus and Cerebral cortex [16]
2	Parkinson's disease (PD)	α-synuclein, Parkin, DJ-1, PINK1(PTEN induced kinase 1), and LRRK2	Basal ganglia and Substantia nigra [17]
3	Huntington's disease (HD)	Huntingtin with expanded polyQ	Basal ganglia [18]
4	Amyotrophic lateral sclerosis (ALS)	SOD1, Ub, p62, FUS, OPTN, TDP-43,ATXN2, UBQLN2, C9ORF72	Motor cortex [19]

TRANSGENIC *DROSOPHILA* TO STUDY NEURODEGENERATIVE DISEASES

Modeling human diseases in animal models and study of the complications

CHAPTER 6

Genetic Basis in Stroke Treatment: Targets of Potent Inhibitors

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Abstract: Stroke is a complex disease resulting from a combination of vascular, environmental and genetic factors. Different therapeutic strategies for the treatment of stroke include antiplatelet therapy, anticoagulants, and lipid- lowering drugs. These drugs act *via* diverse mechanisms of action and target specific enzymes. The enzymes increase the levels of ubiquitous secondary molecules that can cause changes in vascular tone, increase platelet aggregation, cholesterol levels, and other cellular events. Several inhibitors have been developed to curb these enzymes and thus prevent a recurrent stroke. The most potent inhibitors given in the stroke treatment include inhibitors of angiotensin-converting enzyme (ACE) (perindopril, ramipril), phosphodiesterases (PDEs) (rolipram), GpIIb/IIIa and 3-hydroxy-3-methyl-glut-ryl-coenzyme A reductase (HMG-CoA reductase) (pravastatin). ACE inhibitors block the ACE enzyme, thereby preventing the conversion of inactive decapeptide angiotensin I to the active octapeptide and potent vasoconstrictor angiotensin II. Angiotensin II plays a pivotal role in the development of hypertension, atherosclerosis and thrombotic events like stroke. Other inhibitors like phosphodiesterase inhibitors (PDEIs) prevent the inactivation of intracellular mediators of signal transduction such as cAMP and cGMP. These mediators are critical to the regulation of platelet functions. PDEIs are used as antiplatelet agents in clinical settings. Statins are given as lipid-lowering drugs to reduce the risk of stroke by decreasing blood cholesterol levels through inhibition of liver enzyme β-hydroxymethyl glutaryl coenzyme A reductase enzyme. The current chapter will focus on the recent developments in stroke treatment, especially focussing on potent inhibitors such as PDE, ACE, and HMG.

Keywords: Angiotensin-converting enzyme, Compounds, HMG-CoA reductase, Inhibitors, Phosphodiesterase, Platelet activation, Platelet aggregation, SNP, Stroke, Thromboembolism.

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INTRODUCTION

Stroke is a leading cause of death and neurological disability across the world mainly affecting middle aged and elderly population. However, relatively uncommon young stroke cases are also on the rise, decreasing the average age of ischemic stroke onset. The global stroke burden is increasing worldwide; according to the World Health Organization (WHO) stroke and cerebrovascular diseases kill approximately 5.7 million people each year [1]. The prevalence of stroke is reportedly higher in developing countries, resulting in 75.2% of deaths from stroke and 81.0% of stroke-related disability adjusted life years (DALYs) [2]. Patients who suffer a stroke experience one or more physiological symptoms including weakness, numbness, vision loss, speech difficulties, and motor impairment in terms of facial droop, movements of arm and leg of either or both sides of the body. Immediate diagnosis and treatment are of paramount importance as for every minute in an untreated stroke; 2 million neurons die contributing to significant brain damage [3, 4]. The individuals suspected of having a stroke are assessed by a CT scan or MRI. These scans provide clinicians with a screening tool to decide whether the stroke is ischemic or hemorrhagic. These two stroke subtypes have marked clinical differences in their pathogenesis, prognosis, and treatment [5, 6]. Occlusion in an artery or arteriole of the brain blood supply either by thrombosis or an embolus results in an ischemic stroke while the rupture of blood vessel aneurysm or leakage of a weak vessel in the brain leads to hemorrhagic stroke. In both cases, blood flow in the brain is disrupted causing damage to the downstream brain tissue. Ischemic stroke is a predominant subtype that accounts for the approx. 80% of the total stroke cases while the other 20% suffer from hemorrhagic stroke [7]. Based upon the causes of interruption in blood flow through the perforating arteries of the brain, ischemic stroke can be further classified into several distinct subtypes. The Trial of Org 10172 in Acute Stroke Treatment (TOAST) classified ischemic stroke into 5 main etiological subtypes *i.e.* large artery atherosclerosis, small vessel disease, cardioembolic stroke, stroke of undetermined etiology and other determined etiology [8].

Post-Stroke immediate treatment minimizes long-term disability. Current therapeutic agents for stroke include tissue plasminogen activator, antiplatelet agents, anti-hypertension drugs and lipid-lowering drugs [9]. These drugs act *via* diverse mechanisms of action and are centered on the management of modifiable risk factors like hypertension, diabetes, and hyperlipidemia to prevent recurrent stroke events [10]. Stroke is an immensely complex and personalized disease. Researchers have been focussing on determining the genetic basis of the disease, and a substantial body of evidence suggests that numerous candidate genes are implicated in the pathogenesis of ischemic stroke [11]. Variants of these genes are

known to be involved in different pathways like cholesterol biosynthesis, renin-angiotensin aldosterone system (RAS), and cAMP degradation pathway. On account of their crucial molecular role, genes encoding angiotensin-converting enzyme (ACE), phosphodiesterases (PDEs), 3-hydroxy-3-methyl-glutryl-coenzyme A reductase (HMG-CoA reductase) and many more have been identified as plausible biological candidates in the development of ischemic stroke [12 - 14]. The variants of these genes have been identified to promote stroke predisposing mediators, *i.e.* enzymes that actively participate in physiological mechanisms [15]. The use of physiological modifiers in molecular therapeutics has emerged as a big avenue in therapeutics. The current chapter will focus on the recent developments in stroke treatment focusing especially on potent inhibitors of PDEs, ACE and HMG Inhibitors.

PHOSPHODIESTERASE (*PDE)*

PDEs are ubiquitously expressed hydrolases. They catalyze the hydrolysis of the 3',5' phosphodiester bond of cAMP and cGMP to yield 5'-AMP and 5'-GMP, respectively [16 - 19]. The regulation of intracellular cyclic nucleotides takes place by 2 enzymes namely adenylyl cyclase (AC) and PDE [20]. Upon their inability to bind to and activate their effectors including protein kinase A, (which is activated by cAMP), protein kinase G (which is activated by cGMP), cyclic-nucleotide-regulated ion channels (which are activated by cAMP or cGMP) and the guanine nucleotide exchange factor Epac (activated by cAMP) [21], vital downstream physiological and pathophysiological processes like cellular growth, differentiation, proliferation, Ca2-dependent signalling, and inflammation, are affected [22]. PDEs constitute a large and complex superfamily that contains 11 PDE gene families (PDE1 to PDE11), comprising 21 genes that generate approximately or more than 100 proteins by alternative splicing and or multiple promoters [23 - 26]. These isoforms are classified based on their cellular function, primary structures, affinities for cAMP and cGMP, catalytic properties, response to specific activators, inhibitors, effectors and their mechanism of regulation. Tissue- specific distribution of PDEs has facilitated targeted pharmacological inhibition in different diseases (Table **1**). They are considered to be key therapeutic targets, from both clinical and economic purposes. Isoforms of PDE on platelets (PDE2, PDE3, PDE5) and brain tissue (PDE1, PDE4, PDE8, PDE9) offer a novel therapeutic strategy in stroke [27]. PDE4D was among the first isoforms of PDEs known to be implicated in the pathogenesis of stroke. 6 SNPs in PDE4D were found to be significantly associated with ischemic stroke in an Icelandic population [28]. Subsequently, several follow up studies in different ethnic groups were taken up to study the SNPs across this gene for association with the disease. A study carried out in the Chinese population also found a significant association of SNP 83 with the disease where carriers of C allele at

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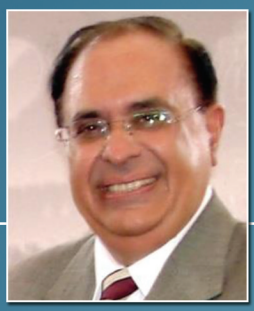

PROF. DR. ATTA-UR-RAHMAN, *FRS*

Prof. Atta-ur-Rahman, Ph.D. in Organic Chemistry from Cambridge University (1968) has 1,232 international publications (45 international patents and 341 books). He received the following awards: Fellow Royal Society (FRS) London (2006), UNESCO Science Prize (1999), Honorary Life Fellow Kings College, Cambridge University (2007), Academician (Foreign Member) Chinese Academy of Sciences (2015), Highest Civil Award for Foreigners of China (Friendship Award, 2014), High Civil Award Austria ("Grosse Goldene Ehrenzeischen am Bande") (2007), Foreign Fellow Chinese Chemical Society (2013), Sc.D. Cambridge University (UK) (1987), TWAS (Italy) Prize (2009). He was the President of Network of Academies of Sciences of Islamic Countries (NASIC), Vice President TWAS (Italy), Foreign Fellow Korean Academy of Science & Technology, President Pakistan Academy of Sciences (2003-2006) and (2011 – 2014). He was the Federal Minister for Science and Technology of Pakistan (2000 – 2002), Federal Minister of Education (2002) and Chairman Higher Education Commission/Federal Minister (2002-2008), Coordinator General of COMSTECH (OIC Ministerial Committee) (1996-2012), and the Editor-in-Chief of Current Medicinal Chemistry.

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Dr. Amtul is a graduate in biochemistry with a specialty in neuroscience. She worked as a Fulbright visiting scholar at the Mayo Clinic Jacksonville, USA while completing her Ph.D. She worked as Alexander von Humboldt Fellow at Heidelberg University, Germany, as Ontario Mental Health Foundation, and the Canadian Institute of Health Research Fellows at Western University, Canada. Currently Dr. Amtul is working as a Senior Faculty Member at Windsor University, Canada. Dr. Amtul's main area of research has been chemical biology and medicinal bioinorganic chemistry. Dr. Amtul has also 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. Lately, she has also started focusing on structural biology, bioinformatics, diagnostics, and drug development to propose novel diagnostics as well as designs of multifactorial neurovascular medicines using optogenetics, decoy, and Trojan horse technologies to treat epilepsy and AD, respectively. Besides teaching anatomy, physiology, and biochemistry, Dr. Amtul has also independently developed and delivered the curriculum of multiple new postgraduate courses in Neuroscience.