Frontiers in Clinical Drug Research

(CNS and Neurological Disorders)

Editors:
Atta-ur-Rahman, *FRS*
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Bentham Books

Frontiers in Clinical Drug Research - CNS and Neurological Disorders

(Volume 9)

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ISSN (Online): 2214-7527

ISSN (Print): 2451-8883

ISBN (Online): 978-1-68108-904-1

ISBN (Print): 978-1-68108-905-8

ISBN (Paperback): 978-1-68108-906-5

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PREFACE

The progressive death of brain neuronal cells is the root cause of several neurodegenerative pathophysiological processes. Once dead, these brain cells cannot then be regenerated. There is an urgent need to dig deeper into the neurodegenerative pathology, identify unexplored markers, and investigate novel therapeutic approaches to identify drugs targets for therapeutics that might improve brain functions and outcomes in the longer run

Volume 9 of our book series *Frontiers in Clinical Drug Research - CNS and Neurological Disorders* showcases another set of state-of-the-art and innovative research ventures produced by the eminent as well as budding scientists in the field of neurodegeneration. They have reviewed, evaluated, and commented to provide a creative futuristic outlook to some of the most exciting latest research findings happening in the field of CNS and Neurological Disorders. This could lead to a better insight into various brain ailments with ground-breaking therapeutic advances and serve as an impetus for future drug development.

Thus chapter 1 explores the possibility of integrated use of microdialysis with expanded use of imaging modalities to better understand and treat Alzheimer's Disease. Chapter 2 highlights the therapeutics targeting immunometabolic dysregulations to benefit patients with atypical depression. It also proposes the use of a transdiagnostic dimensional approach to capture the complexity of mood disorders by incorporating the pathophysiological and clinical data and considers the influence of neurodevelopmental and environmental factors. Chapter 3 summarizes the basics of chimeric antigen receptor (CAR)-T therapy and discusses its current pre-clinical and clinical progress and applications in brain tumors and autoimmune diseases. Chapter 4 discusses the efficacy of thyrotropin-releasing hormone (TRH) and its various mimetics to treat various neurological and psychiatric disorders, such as spinocerebellar degeneration (SCD), cognitive impairment, and Alzheimer's disease given by non-oral routes. Chapter 5 reviews the role of beta-site amyloid precursor protein-cleaving enzyme-1 (BACE1) in cognitive decline associated with Alzheimer's disease, and investigates the use of natural plant extracts and phytoconstituents as BACE1 inhibitors. Chapter 6 analyses the anxiolytic and adaptogenic effects of a new drug, a complex of lithium citrate and a sorbent (aluminum oxide and polydimethylsiloxane or lithium complex) to target cognitive impairment in experimental animals via a course of preclinical studies. Chapter7 evaluates the therapeutic potential of approved disease-modifying therapies (DMTs) to address the acute relapse of multiple sclerosis (MS).

In short, the current volume presents a scholarly collection of review articles to advance the field further. It is anticipated that the compiled views and reviews as well as the critical analysis will drive further research in the area to provide avenues for future drug exploration not only in the field of neuroscience but also in a vast majority of other science disciplines.

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

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CHAPTER 1

Integrating Imaging and Microdialysis into Systems Neuropharmacology

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Abstract: Microdialysis sampling has been coupled with several imaging modalities over the past two decades to either support the development of imaging approaches as diagnostic, prognostic or treatment response biomarkers, or to use this temporally rich sampling approach of brain tissue in parallel with one or more imaging modalities to provide an integrated, systems neuropharmacology, perspective of normal and diseased brain physiology. This chapter provides a comprehensive review of the scientific literature that encompasses several imaging modalities (including PET, MRI, EEG, CT) that relied on microdialysis sampling for its supportive and/or parallel use in systems neuropharmacology research. A review of the important role microdialysis has played in supporting several PET imaging applications used in neuropharmacology research is provided. Integrated with PET, various MRI modalities, EEG and CT, microdialysis has deepened understanding of various neurotransmitter systems and their temporal and spatial integration as an in-tune, "normal" or dysynchronous, "diseased" system. Parallel use of microdialysis in humans suffering from traumatic brain injury or chronic epilepsy has been coupled with PET, MRI, EEG and CT approaches to develop systems-level understanding at the cellular, regional, and whole brain levels. Throughout the chapter, several publications are discussed that exemplify the results of this research. The chapter concludes with a presentation of the integrated use of microdialysis with imaging in Alzheimer's Disease research, ending with the hope for expanded use of imaging modalities that can even be used in an ambulatory capacity, and how microdialysis can continue to play its established role to support their development and use in understanding and treating this disease.

Keywords: Alzheimer disease, Blood-brain barrier, Brain, Brain injuries, Central nervous system, Electroencephalography, Magnetic resonance imaging, Microdialysis, Neuropharmacology, Positron-emission tomography, Tomography.

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INTRODUCTION

It is truly remarkable when one considers the brain's ability to coordinate its myriad activities, such as, to code dynamic visual cues into behavior, or to retrieve information at a moment's notice and build upon it to create new learning, or to instantly recognize a familiar face or voice. Perhaps it is even more remarkable that these integrated activities are a consequence of a system that operates through electrochemical and chemical mechanisms that encompass spatial and temporal continuums from the subcellular and microsecond domains to circuits composed of circuits that can remain constant over a lifetime. At both the anatomic and functional levels, the healthy brain is a highly integrated system that exhibits remarkable adaptability over decades of life. Our understanding of this system at these two levels is arguably rudimentary, thus dedication to continuous development and refinement of experimental and computational tools that can describe circuit anatomy at local and regional levels, and then relate these in a cause-effect way to circuit function in healthy and diseased brain is worthy. Positron emission tomography (PET) and magnetic resonance imaging (MRI) have demonstrated power as non-clinical and clinical approaches to evaluate non-invasively the anatomic and functional circuitry of the brain. While use of these tools in living animals and humans has continued to improve over the last 20 years, the need for advances remains. An objective of this chapter is to describe how microdialysis, as an *in vivo* sampling method, has advanced the application of these imaging approaches. The chapter will present microdialysis as a supportive tool enabling application of imaging modalities as biomarkers to inform disease diagnosis and prognosis, and support the development of new treatments for human brain diseases. In addition, microdialysis sampling is a proven and important independent technique in preclinical neuropharmacology research; accordingly, this chapter will present examples of its parallel use with various imaging modalities in a pre- or non-clinical environment to inform systems neuropharmacology.

The chapter will first provide an overview of the microdialysis sampling method and its use in neuropharmacology, including general support of drug discovery and development, and lastly, its use in humans in a specific way to inform treatment of traumatic brain injury. A PubMed survey of the literature coupled 'microdialysis' with various imaging modality keywords. These included computed tomography (CT), electroencephalography (EEG), PET, single-photon emission computed spectroscopy (SPECT), MRI, optical imaging, fluorescence, near-infrared spectroscopy (NIRS), and mass spectrometry imaging (MSI). The survey identified several examples using microdialysis with PET, MRI or EEG, thus separate sections devoted to the use of microdialysis alongside these imaging modalities will follow the microdialysis overview. There will then be a brief

section on integration of microdialysis with other, less frequently used, imaging modalities. The chapter will conclude with a section devoted to Alzheimer's disease research. This last section represents a change in focus from one of microdialysis use with specific imaging modalities to a discussion of how all modalities and microdialysis have been and conceivably could be used to inform research whose overarching objective is to discover therapies to address this devastating disease.

MICRODIALYSIS OVERVIEW

More than 100 billion neurons and non-neuronal cells comprise the human brain [1], and are bathed by an interstitial fluid commonly referred to as the brain extracellular fluid (ECF). Through this fluid, cells communicate *via* the release of neurotransmitters and neuromodulators. Microdialysis enables direct sampling of ECF in a living organism; when coupled to an analytical technique, it provides a means to identify and measure these released chemicals and associated metabolites. Fig. (**1**) is a diagram of a concentric microdialysis probe commonly used in CNS research. The dialysis membrane is a key component of the probe, composed of a porous membrane, cellulose or polyether-based, and varying in pore size. Commercially available membrane pore sizes commonly span molecular weight cut-offs ranging from 6 – 100 kilodaltons. Typical perfusion flow rates range from 0.5 – 2.0 µL/min, with typical collection times of 10 – 30 minutes.

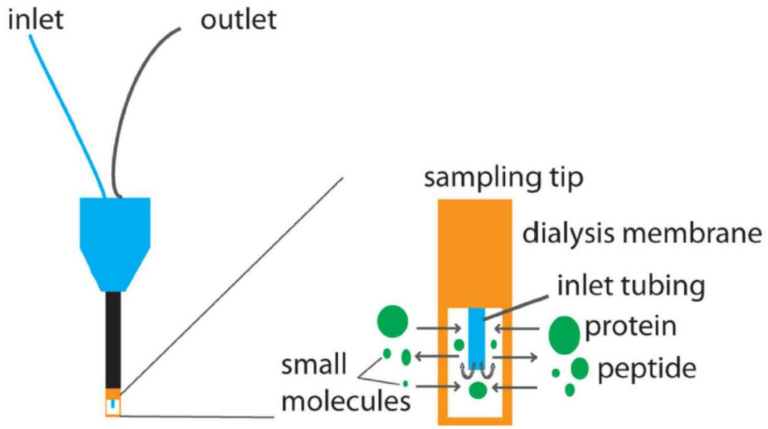

Fig. (1). Diagram of a concentric microdialysis probe design commonly used in CNS microdialysis. The term "concentric" refers to two cylinders: a smaller cylinder delivering fluid into the probe tip ("inlet") fitting inside a larger cylinder that carries fluid (dialysate) away from the tip (outlet) for subsequent analysis of solutes. Fig. obtained by permission from publisher of Fig. 6 in OuYang C, Liang, Z and Li L. 2015. Mass spectrometric analysis of spatio-temporal dynamics of crustacean neuropeptides. Biochim Biophys Acta 1854 (7): 798-811.

CHAPTER 2

Depression Heterogeneity and the Potential of a Transdiagnostic and Dimensional Approach to Identify Biologically Relevant Phenotypes

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Abstract: Major depressive disorder (MDD) is the most prevalent mood disorder worldwide and the third leading cause for years lived with disability. Major challenges encountered in the treatment of MDD include high non-responder and relapse rates and delayed therapeutic onset. MDD is a heterogeneous condition, and the identification of more homogenous groups of patients may facilitate the selection of optimal therapeutic strategies. Different approaches have been considered for the subtyping of depression, including etiological factors, clinical symptoms, biological markers, and treatment response. However, the optimal strategy for the identification of more homogenous groups of patients remains elusive. In this chapter, the subdivision of depression into melancholic and atypical subtypes, the significance of considering hypomanic or manic symptoms in the diagnosis and treatment of depression, and the importance of combining biological and clinical findings based on the approach implemented by the Research Domain Criteria (RDoC) project are discussed. Phenotypic associations between atypical depressive symptoms and obesity-related traits have also been identified that may arise from shared pathophysiologic mechanisms. Thus, the development of treatments effectively targeting immunometabolic dysregulations may benefit patients with atypical depression. The presence of hypomanic or manic symptoms in patients with depression may be relevant for the selection of a therapeutic strategy. Notably, the longitudinal course of mood-related symptoms should be considered, and a dimensional approach should be applied to capture the complexity of mood disorders. The application of the RDoC framework to mood-related symptoms allows the use of a transdiagnostic dimensional approach, which incorporates pathophysiological and clinical data and considers the influence of neurodevelopmental and environmental factors. Future studies on MDD subtypes and more broadly defined mood-related symptoms should focus on the identification of biologically relevant disease phenotypes and take into account the role of neurodevelopmental and environmental factors for the identification of new therapeutic targets.

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Keywords: Atypical depression, Biomarkers, Data-driven phenotypes, Depression subtypes, Hypomanic symptoms, Major depressive disorder, RDoC.

INTRODUCTION

Major depressive disorder (MDD) is the most prevalent mood disorder worldwide, affecting almost 322 million individuals [1]. It has a lifetime prevalence of 16.6% and is considered the third leading cause for years lived with disability [2, 3]. MDD is characterized by the presence of depressed mood and loss of pleasure or interest that last for at least 2 weeks. At least three of the following additional symptoms should also be present on most days for an MDD diagnosis: hypersomnia or insomnia, a change in appetite or weight loss, loss of energy or fatigue, psychomotor retardation, or agitation, feelings of worthlessness or excessive guilt, impaired ability to concentrate or think or indecisiveness, and recurrent thoughts regarding death or suicidal ideation, plan, or attempt [4].

Antidepressant medications, psychotherapy, or a combination of antidepressant medications and psychotherapy are first-line treatments for MDD [5]. Physicians generally select between a second-generation antidepressant and/or cognitive behavioral therapy as treatment options. A number of factors may influence the selection of a treatment strategy, including treatment effects, safety profiles, accessibility, cost, and patient preferences [5].

However, the efficacy of pharmacological and non-pharmacological therapeutic approaches for depression is limited by high non-responder and relapse rates. Only 60%–70% of patients respond to antidepressant therapy. Moreover, the onset of action of antidepressant treatment is delayed, which further underscores the need to develop improved therapeutic strategies for MDD [6].

THE HETEROGENEITY OF MAJOR DEPRESSIVE DISORDER

There is a consensus that MDD is a heterogenous disorder [7, 8]. The idea that the identification of more homogenous MDD subtypes may facilitate the development of improved therapeutic agents is being actively investigated. The heterogeneity of depression has been evaluated on different levels, including its etiological factors, clinical symptoms, biological markers, and treatment response. A meta-review assessed the published reviews on the heterogeneity of depression. It identified five categories of depression subtypes: symptom-based subtypes, etiologically-based subtypes, time of onset-based subtypes, gender-based subtypes, and treatment-resistant depression [9]. Within the scope of symptomatology-based approaches, melancholic and atypical depression, as well as the presence of hypomanic or manic symptoms, have been frequently investigated; notably, the presence of both atypical features and hypomanic

symptoms in patients with MDD has been associated with increased recurrence rates [10]. Data-driven approaches have also been used to identify depression subtypes [11 - 13]. However, the optimal strategy for the determination of biologically relevant depression subtypes has not been identified yet. The transdiagnostic dimensional Research Domain Criteria (RDoC) framework launched by the National Institute of Mental Health (NIMH) implements a different approach. It combines pathophysiological and clinical data to identify human functional domains implicated in mental disorders and gain insight into the mechanisms and potential treatment strategies for mental disorders [14].

This book chapter discusses several different approaches for the identification of depression subtypes and their utility and limitations. In particular, it reviews the subdivision of depression into melancholic and atypical subtypes, the significance of assessing hypomanic or manic symptoms in the diagnosis and treatment of depression, and the importance of combining biological and clinical findings based on the approach proposed by the RDoC project.

MELANCHOLIC AND ATYPICAL DEPRESSION

Melancholic and atypical depression are MDD subtypes with partially distinct symptom profiles. Melancholic depression is characterized by depressed and non-reactive mood, loss of pleasure in activities, and psychomotor disturbances. Various definitions for atypical depression have been proposed. The term “atypical depressive state” was used for the first time by West & Dally in 1959 to describe patients with somewhat atypical depression symptoms that responded well to the monoamine oxidase (MAO) inhibitor iproniazid [15]. In 1994, the term atypical depression was introduced to describe a specific set of MDD symptoms included in the Diagnostic and Statistical Manual of Mental Disorders (DMS)-IV. In atypical depression, depressed mood improves in response to positive events, sleep and appetite are increased, there is an associated weight gain, and rejection sensitivity in interpersonal interactions and leaden paralysis are common [16]. Latent class analyses of data from a national comorbidity survey and a twin registry confirmed the existence of typical and atypical depression classes and of depression classes with different severity [17, 18]. In accordance with these findings, a latent class analysis of patients with depression enrolled in the Netherlands Study of Depression and Anxiety (NESDA) identified a severe melancholic class, a severe atypical class, and a class with moderate severity with prevalence rates of 46.3%, 24.6%, and 29.1%, respectively [19]. This study also identified both the symptom profile (melancholic and atypical depressive symptoms) and disease severity as important factors for the identification of depression subtypes. Melancholic features and atypical features have been included in the DSM-5 as two of the specifiers of MDD [4]. Atypical depression

CHAPTER 3

CAR-T Cells in Brain Tumors and Autoimmune Diseases – from Basics to the Clinic

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Abstract: Chimeric antigen receptor (CAR)-T cell therapy has recently been introduced as a promising therapeutic T cell-based therapy. Autologous T cells are collected from the patient, engineered *in vitro* to express artificial chimeric receptors against a specific tumor antigen, and infused into the patient. The success of adoptive CAR-T cells for cancer immunotherapies, particularly in hematological malignancies, inspired researchers of the field. These armored T cells also showed a great potential to be used in the treatment of pediatric brain tumors and autoimmune diseases. In this chapter, we summarize the basics and developments of CAR-T cells from our previous review articles and then discuss the current progress in the pre-clinical and clinical application of CAR-T cells in brain tumors and autoimmune diseases.

Keywords: Adoptive cell therapy, Autoimmune disease, Brain tumor, Cancer immunotherapy, CAAR, CAR-T, Glioblastoma, Regulatory T cell, Tumor antigen.

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1. INTRODUCTION

In adoptive cell therapy (ACT), the immune cells, especially T cells, engaged in the anti-tumor responses are harvested from cancer patients and infused back to the patients following expansion and selection or *ex vivo* modification. This type of immunotherapy increased greater consideration when tumor-infiltrating lymphocytes (TILs) corroborated promising effects in the sufferers with metastatic melanoma (response rates of over 50% and durable complete response rates of 20%), and infusion of the greater population of TILs was indicated to be correlated with more favorable prognosis [1, 2]. Administration of Kymriah® and Yescarta®, FDA approved chimeric antigen receptor (CAR) T cell therapies in hematological malignancies, displayed complete response rates in more than 80% of patients [3, 4]. Accordingly, so-called 'living drugs', referring to the next-generation ACTs using genetically manipulated immune cells, promptly replaced the traditional ACT. Nevertheless, the individuals' T cells, either CD4+ or CD8+ T cells, are segregated and engineered/enriched to specifically assault cancer cells in all T cell therapies Fig. (**1**).

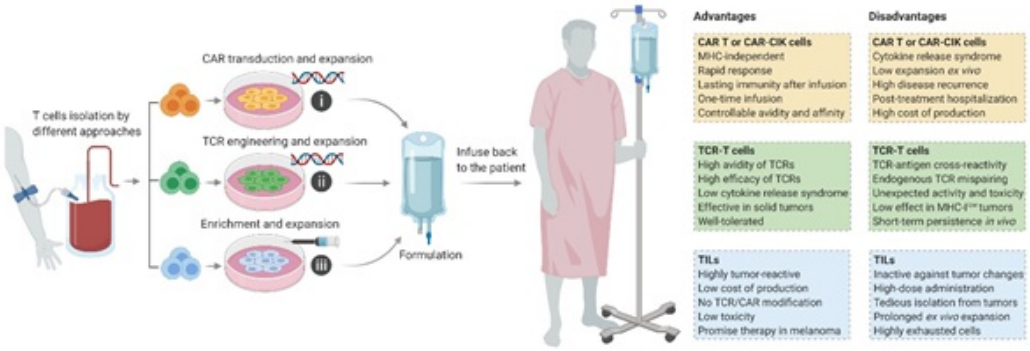

Fig. (1). Different T cell-based immunotherapies. Advantages and disadvantages of therapy strategies base on T cells, including (i) chimeric antigen receptor (CAR) T or CAR cytokine-induced killer (CAR-CIK) cells, (ii) TCR-engineered T (TCR-T) cells, and (iii) conventional tumor-infiltrating lymphocytes (TILs). The principal step during the manufacturing procedure of CAR T/CIK cell therapy, TCR-T therapy, and conventional TIL therapy is CAR transduction, TCR engineering, and TIL enrichment, respectively. The figure is from [5].

A single-chain variable fragment (scFv) which is directed against tumor cell antigen, and intracellular signaling domains from CD3ζ plus a co-stimulatory molecule, commonly CD28 or 4-1BB (CD137), are the main component of CARs, as hybrid transmembrane receptors, which make CAR-T cells independent of major histocompatibility complex (MHC). MHC-independency is the most important distinctive feature of CAR-T cells compared to T cell receptor (TCR) engineered T cells (TCR-T cells). Notably, 'signal 2' needed for T cell expansion

and persistence is provided by the intracellular domains of 4-1BB (CD137) and/or CD28 co-stimulatory elements, whereas, 'signal 1' that is associated with T cell activation, is induced through the TCR CD3ζ chain [5]. As described above, unlike TCRs, CARs are MHC-independent, chiefly play the role of an antibody detecting unprocessed surface-embedded antigens such as proteins, glycolipids, and carbohydrates. Indeed, the combination of the great affinity and specificity of an antibody with the TCR intracellular signaling is the dominant idea behind CAR-T cells Fig. (**2**). Recently, treatment of cancer patients based on stimulation of tumor antigen-specific immune response has been applied in numerous clinical trials using CAR-T cells. Safety, effectiveness, and antigen specificity are the major characteristics that have been endowed to T cells by new generations of CAR-T cells (reviewed in [6]).

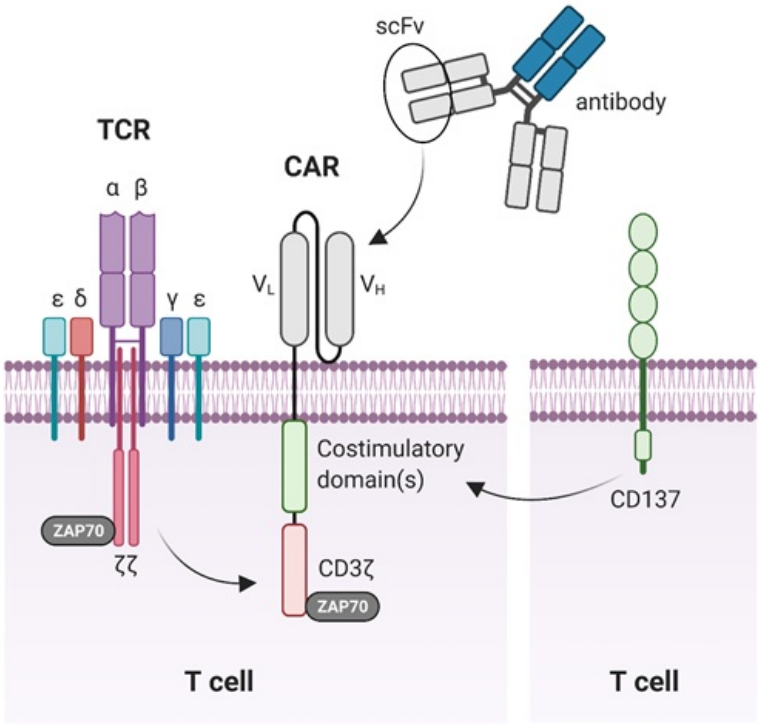

Fig. (2). Basic differences between TCRs and CARs. TCRs (left) contain an αβ heterodimer and CD3 sub-domains that link to the antigenic epitope in an MHC-dependent manner, whereas CARs (right) are chimeric molecules composing of an scFv capable of interacting with cell surface antigens, co-stimulatory domain(s) (usually CD28 or CD137), and intracellular domain of CD3ζ conducting down-stream signaling pathways in an MHC-independent mode of action like antibodies. Both TCRs and CARs mediate downstream signaling by linking to the ZAP70.

CHAPTER 4

Revaluation of Thyrotropin-Releasing Hormone and Its Mimetics as Candidates for Treating a Wide Range of Neurological and Psychiatric Disorders

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Abstract: Thyrotropin-releasing hormone (TRH) is a neuropeptide having many biological and pharmacological activities. TRH (protirelin tartrate) has been used for the treatment of persistent disturbance of consciousness disorder because of its amelioratory effect. However, therapeutic use of TRH entails problems, such as its low lipophilicity, short half-life times due to specific degradation enzymes, and low penetration of the blood-brain barrier (BBB) for access to the central nervous system (CNS). To overcome such problems, a large number of TRH mimetics have been developed for the treatment of various neurological and psychiatric disorders, including spinocerebellar degeneration (SCD), cognitive impairment, and Alzheimer's disease (AD), given by non-oral routes such as intravenous (iv) administration. However, orally effective TRH mimetics are needed to help improve the quality of life (QOL) of patients. As the first orally active TRH mimetic for the treatment of SCD, Taltirelin (Ceredist) has been launched in Japan for administration twice a day. Recently, rovatirelin reported to have high oral bioavailability (BA), was developed for SCD as a potentially effective treatment option in clinical trials by oral administration once a day. This would allow treatment with TRH and its mimetics to be moved from the hospital to outpatient or homecare facilities, and their use for a wider range of disorders. In the near future, TRH and its mimetics should become available as one of the key treatments for various neurological and psychiatric conditions, such as AD, Parkinson's disease (PD), depression and so on.

Keywords: Alzheimer's disease, Amyotrophic lateral sclerosis, Bioavailability, Blood-brain barrier, Central nervous system effect, Clinical trials, Depression,

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Drug delivery system, Endocrine effect, Epilepsy, Lipophilicity, Mimetic, Orally effective, Pain, Parkinson's disease, Peptide, Sleep disorder, Specific degradation enzyme, Spinocerebellar degeneration, Thyrotropin-releasing hormone.

INTRODUCTION

What is Thyrotropin-Releasing Hormone?

Thyrotropin-releasing hormone (TRH, thyroliberine or protirelin), a hypothalamus hormone, was isolated from pigs and sheep [1, 2]. It is a neuropeptide comprised of three amino acids with the chemical structure of pyroglutamyl-histidy--prolinamide (pGlu-His-Pro-NH_2) Fig. (**1**).

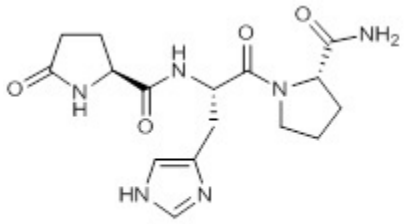

Fig. (1). Chemical structure of TRH.

TRH is biosynthesized as prepro-TRH (Lys-Arg-Gln-His-Pro-Gly-Lys-Arg) after transcription. The pairs of Lys-Arg residues of prepro-TRH are cleaved by carboxypeptidase E to generate pro-TRH (Gln-His-Pro-Gly). The prolylglycine (Pro-Gly) residues of pro-TRH are converted to prolinamide (Pro-NH_2) by peptidylglycine α-amidating monooxygenase to produce the intermediate Gln-His-Pro-NH_2. Finally, conversion of the glutamine (Gln) residue to the pyroglutamic acid (pGlu) residue is accomplished by glutaminyl cyclase (QC) and generates TRH [3 - 5]. TRH is distributed throughout the brain and its periphery. It is present in the hypothalamus, pituitary, cerebellum, and hippocampus, as well as the spinal cord, pancreas and gastrointestinal tract [6 - 8]. TRH has the important role of being a central regulator of the hypothalamic-pituitary-thyroid (HPT) axis [9]. The biological activities of TRH can be classified into two main categories, central nervous system (CNS) and endocrinological effect. TRH and TRH mimetics are being developed to treat several CNS disorders. TRH shows high water solubility, but significantly low lipophilicity (clog P = −2.8) [10]. Therefore, it shows low biological availability from the intestine and from the brain as it must pass through the blood-brain barrier (BBB). Also, the half-life time ($t_{1/2}$) of TRH is within 5 min after intravenous (iv) administration because it is degraded at the pyroglutamate or prolinamide residue by specific enzymes [11].

This has led to the research and development of a large number of TRH mimetics in order to find those effective TRH mimetics for the treatment of CNS and neurological disorders. Among them, taltirelin hydrate (Ceredist) has been launched in Japan as an oral agent for the treatment of spinocerebellar degeneration (SCD). This chapter presents collates information from previous reviews to suggest TRH and TRH mimetics as drugs with the possibility of being developed for the treatment of CNS disorders [12, 13]. Moreover, article informations of TRH and TRH mimetics were used mainly through journal databases, PubMed, ScienceDirect and SciFinder.

TRH Receptors

All effects of TRH are mediated *via* specific receptors (TRH-R), which are G-protein coupled receptor (GPCR) with calcium or inositol serving as mediators [14]. The known intracellular TRH signaling pathways are shown in Fig. (**2**) [15 - 18]. Here, the squares represent compounds, ions and receptors and the ellipses show proteins related to TRH signal pathways. After TRH binds to TRH-R, phospholipase C-β (PLC-β) is activated and allows the hydrolysis of phosphatidylinositol 4,5-P2 (PIP2) to produce inositol-1,4,5-triphosphate (InsP3) and 1,2-diacylglycerol (DAG). These second messengers activate the protein kinase C (PKC) [19] and subsequently increase the intracellular calcium cation (Ca^{2+}) level. Ca^{2+} binds to calcium/calmodulin-dependent protein kinase (CamKin) [20] and forms the Ca^{2+}-CamKin complex. This complex activates the transcription factor, a cyclic AMP (cAMP) responsive element binding protein (CREB) [21]. PKC activates the transcription factor, activating protein-1 (AP-1) [22]. On the other hand, the signal from TRH-R stimulates mitogen-activated protein kinase (MAPK) [23] or extracellular signal-regulated kinase 1/2 (ERK1/2) [24]. These kinases activate the transcription factor, ETS-like gene-1 (Elk-1) [25].

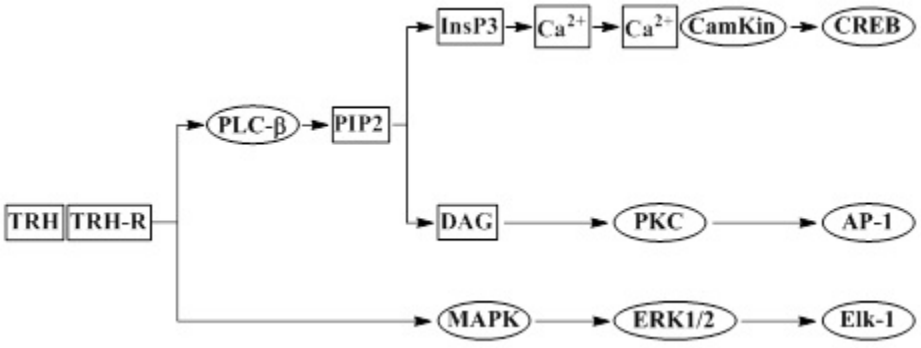

Fig. (2). Intracellular TRH signaling pathways.

CHAPTER 5

Natural BACE1 Inhibitors: Promising Drugs for the Management of Alzheimer's Disease

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Abstract: Alzheimer's disease (AD) is characterized by impaired cognitive functions due to irreversible neuronal injury by the formation of abnormal beta-amyloid plaques (aggregated amyloid beta-peptide (AβP)) in the brain. Among various secretase enzymes, beta-site amyloid precursor protein-cleaving enzyme-1 (BACE1) functions in the first step and is the rate-limiting step of the AβP formation. Therefore, BACE1 has attained considerable attention as a novel therapeutic target for the management of AD. Inhibition of BACE1 prevents the generation of amyloid-beta and hence blocks the impending pathological events that occur due to beta peptide accumulation. The drugs being used clinically (acetylcholinesterase inhibitors and NMDA receptor antagonists) so far have not been able to cure AD completely and are associated with a high risk of toxicity. Thus, finding a newer therapeutic regimen for AD is of utmost importance and BACE1 could be a potential target for developing newer drugs.

Plants are described as memory enhancers in various ancient systems of medicines, including Ayurveda and Traditional Chinese System, and thus, are being used by mankind for improving intellect skills and cognition. Recently, research has paid much attention to the drugs of natural origin as these are generally considered safe and devoid of side effects. Therefore, herbal extracts are explored for specific BACE1 inhibitory activity, and compounds (BACE1 inhibitors) are isolated. There are several plant extracts and phytoconstituents that have demonstrated marked BACE1 inhibitor activity along with superior biosafety. This chapter highlights the role of BACE1 in the pathogenesis of memory deficit associated with AD and draws attention to the distinct potential natural BACE1 inhibitors for AD treatment.

Keywords: Alzheimer's disease, Amyloid-beta, BACE 1, Clinical trials, Cognitive impairment, Flavonoids, Natural products, Neurodegeneration, Novel target, Phenols.

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INTRODUCTION

With the increase in the number of cases of Alzheimer's disease (AD), there is an upsurge in the need for disease-modifying therapies. AD accounts for the most common subtype of dementia in the late stages of life, mainly in persons more than 60 years of age [1]. The disease leads to a neuropathic condition that causes mental, behavioral, and functional deterioration. AD involves both neurochemical (acetylcholine, dopamine, noradrenaline, and serotonin) and neurohistological modifications in specific regions of the brain that is responsible for cognitive and psychological symptoms [2 - 4]. Neuritic plaques (NP's) and neurofibrillary tangles (NFT's) symbolize the two major pathological hallmarks of AD. NP's are generated by the accretion of amyloid-beta peptide (Aβ) in brain tissues whereas hyperphosphorylation of microtubule-associated Tau protein in neurons leads to the formation of NFT's [5]. Disturbance in neurotransmitter levels, specifically acetylcholine, which is involved in learning, is also a causative factor for the disease [6].

Earlier the treatment of AD was grounded on the "cholinergic hypothesis" which testifies that cognitive impairment in AD is the outcome of abnormalities in the acetylcholine system [7]. Currently, FDA-approved therapy for AD consists of four AChE inhibitors: rivastigmine, donepezil, galantamine, and tacrine and an NMDA receptor antagonist, memantine [8]. All these drugs are helpful in providing symptomatic relief but they are not able to fully alleviate the disease. The researchers then shifted towards remedies addressing amyloid cascade in order to find a therapy that can obstruct the advancement of AD [9]. The present chapter attempts to explain the role of beta-site amyloid precursor protein cleaving enzyme 1 (BACE1), a vital enzyme involved in proteolytic cleavage of the amyloid precursor protein, in the pathogenesis of AD and to reveal the potential natural BACE1 inhibitors that could be developed as potential neurotherapeutics for the management of AD.

THE IMPLICATION OF BACE1 IN AD PATHOGENESIS

The aspartic residues, which are considered to be active site motifs, are located at positions 93 and 289 that are said to be responsible for proteolytic activity [11]. The enzyme is accountable for the cleavage of APP to form the N-terminus of Aβ peptide and membrane-bound carboxy-terminal fragment, C99. After that γ-secretase cleaves the C-99 fragment to generate the C-terminus of Aβ and the mature peptide Fig. (**1**). The peptide is released in the interstitial fluid of the brain, thus initiating various pathogenic pathways which latterly lead to dementia.

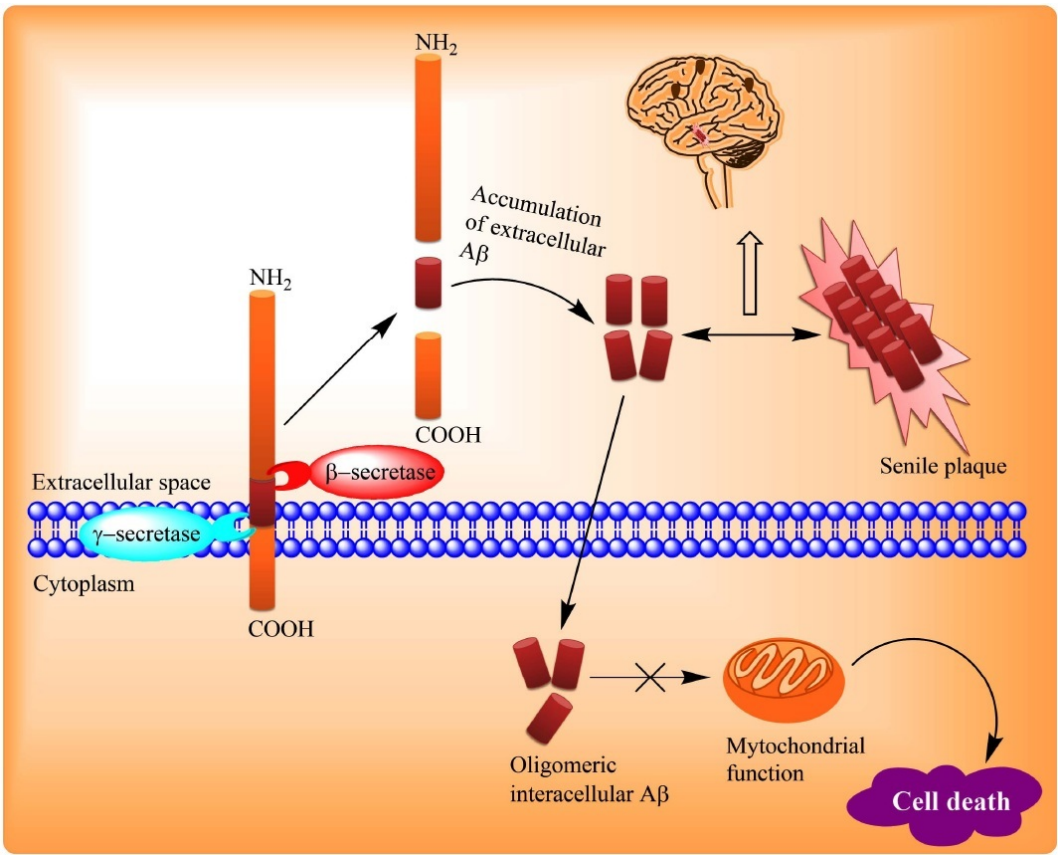

Fig. (1). Role of BACE1 in the pathogenesis of AD.

Beta secretase was identified autonomously by five different groups of researchers in the year 1999 as β-site amyloid precursor protein (APP) cleaving enzyme 1 (BACE1), also called Asp2 and memapsin2. BACE1 is a 501 amino acid type I transmembrane aspartic protease associated with pepsin and retroviral aspartic protease families. The various subdomains of the enzyme, given in Fig. (**2**), are as follows:

- N-terminal signal peptide consisting of 23 amino acids.
- Propeptide domain having 23-48 amino acids.
- Catalytic domain with 48-421 amino acid.
- The loop consisting of 421-454 amino acids.
- Transmembrane domain having 454-478 amino acids.
- Cytosolic queue with 23 amino acids [10].

CHAPTER 6

The Possibilities of Safe Lithium Therapy in the Treatment of Neurological and Psychoemotional Disorders

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Abstract: Lithium is a type of psychotropic drug, belonging to the normothymics classification group. It is used in the treatment of affective disorders such as manic and hypomanic phases of bipolar disorder and severe and treatment-resistant depression. It also has anti-suicidal properties and a neuroprotective effect on neurodegenerative diseases. This article presents findings regarding the effects of lithium in experimental pathology of the central nervous system in mice and rats. In clinical practice, lithium is the standard for pharmacological treatment of bipolar disorders. The drug is also effective in treating depression. It suppresses aggressiveness and is a therapeutic agent in the treatment of chronic neurodegenerative diseases such as Alzheimer's, Parkinson's and Huntington's disease. Lithium salts however can be highly toxic even in relatively low doses. The mechanism of action of lithium salts can be realized through the inhibition of glycogen synthase kinase -3β (GSK-3β) and inositol monophosphatase 1 (IMAP1). Inhibition of GSK-3β is considered to be one of the fundamental mechanisms in the implementation of the action of lithium ions on the body. Lithium stabilizes adenylate cyclase activity and acts as an antagonist of sodium ions in nerve and muscle cells. One of the ways to deliver lithium to target organs is to combine lithium salts with a sorbent (a solid porous carrier). This approach made it possible to create modified sorbents for the prolonged delivery of components such as lithium and silver. A new drug – a complex of lithium citrate and a sorbent – aluminum oxide and polydimethylsiloxane (lithium complex) was created at the Research Institute of Clinical and Experimental Lymphology – a branch of the Institute of Cytology and Genetics SB RAS. Its anxiolytic and adaptogenic effects were observed over the course of preclinical studies. The lithium complex improved cognitive functions in experimental animals, influenced the electrophysiological activity of the brain and had positive effects on the behavior of mice in the experimental model of chronic social

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stress. The lithium complex is therefore a promising drug for the treatment of neurological and psychoemotional disorders.

Keywords: Aluminum oxide, Aggression, Alcohol, Anxiety-depressive disorder, Behavior, Brain electrophysiology, Conditioned reflex, Caffeine, Depression, Enterosorbent, Lithium, Lithium toxicity, Mice, Normothymic drug, Physical performance, Polydimethylsilloxane, Prevention, Rats, Serotonin, Serotonin receptors.

INTRODUCTION

Lithium (lat. *Lithium, Li*) is a chemical element belonging to the first group of the Periodic Table, with an atomic number of 3, atomic mass of 6.941, and part of the alkali metals group. Natural lithium consists of two stable isotopes - ^{6}Li (7.42%) and ^{7}Li (92.58%). Lithium was discovered in 1817 by Swedish chemist Johan August Arfwedson in the mineral petalite; the name comes from the Greek *lithos* – meaning 'stone'. Lithium metal was first obtained in 1818 by English chemist Humphry Davy. The distribution of lithium in nature, its physicochemical properties, production and application in technology are well studied at the present time. A chemically simple ion, which continues to find its important applications in biology and medicine was presented [1, 2].

Lithium is a type of psychotropic drug, belonging to the normothymics classification group. Historically, it was the first drug of this group, discovered in 1949, and remains essential in the treatment of affective disorders, primarily manic and hypomanic phases of bipolar disorder, as well as in the prevention of its exacerbations and for the treatment of severe and treatment-resistant depression, possessing properties to help prevent suicide and have a neuroprotective effect on neurodegenerative diseases [3].

Lithium takes part in many important processes in the body; it is involved in fat and carbohydrate metabolism [4], prevents allergies [5], supports the functioning of the immune system [6], neutralizes the effects of alcohol, heavy metal salts and radiation. Other medicinal properties of lithium have also been found; it can prevent the development of atherosclerosis and cardiovascular diseases [7] and reduce the likelihood of developing hypertension and diabetes [8], however this requires interaction with other minerals and vitamins as substances can be absorbed by the body only in the case of a balanced intake. Lithium also affects the hematopoietic system and can be used in the treatment of leukemia [9].

In medical practice, water-insoluble lithium carbonate in the form of a standard tablet has been widely used. Other forms such as lithium salts and delivery

methods into the body are also of great interest. One of them is associated with the use of solid porous sorbents, which play the role of carriers for the delivery of lithium ions in the desired direction.

It should be noted that at present, various types of sorbents have been developed, such as coal, organosilicon, carbon-mineral, modified [10]. They differ in shape, porous structure, chemical nature of the matrix, and in the type of interaction with the sorbate. Not only their medicinal properties, but also their protective, cell-saving effects for restorative medicine have been noted. Due to the developed porous structure and certain chemical nature of the surface, sorbents are a convenient way to deliver biologically active substances into the human body [10. 11]. Various treatment programs that promote the use of sorbents have been developed and introduced into practical medicine, some of which use sorbents as protectors of body homeostasis violations. The use of sorption therapy also allows the prevention of diseases. Sorbents are widely used in medical practice to detoxify the body to help prevent and treat various diseases. The wellness effect of sorbents can be enhanced if biologically active substances (enzymes, cells, and so on) are applied to their surface. The sorbent would then act simultaneously as a carrier for the delivery of active substances, for example, to the necessary parts of the gastrointestinal tract, as well as a detoxifier. This approach made it possible to create modified sorbents for the prolonged delivery of components such as lithium [12]. Such a technique is especially important when the drugs are substances which tend to be rapidly absorbed, for example, lithium salts. The large list of diseases, for which sorption technologies are recommended, also contains neuropsychiatric and mental diseases. It is well known that lithium is crucial for the correction of psychoemotional states. The overview [13] presents the results of a study of the effectiveness of lithium salts across a number of neurological diseases in humans (bipolar disorder, stroke, amyotrophic lateral sclerosis, and others), which indicates the high clinical significance of studying the mechanisms of action of this drug.

In medicine, lithium is used in the form of salts, mainly in the form of carbonate, as well as citrate, succinate, orotate, chloride and lithium sulfate. As mentioned above, the most widely used lithium drug is lithium carbonate [14].

MECHANISM OF ACTION OF LITHIUM MEDICATIONS

Currently, two possible mechanisms of influence of lithium salts dominate: inhibition GSK-3β and IMAP1.

The targets of lithium action are considered to be two different signaling pathways with two different enzymes underlying their functioning. Historically,

CHAPTER 7

Pharmacotherapy of Multiple Sclerosis and Treatment Strategies

Amany Ragab[1,*], Ali Ibrahim[2], Rania Helal[3], Ahmed Elsaid[4], Hossam Younis[5], Mona Elsherbiny[6] and **Takwa Elkhatib[7]**

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Abstract: Multiple sclerosis (MS) is a well-known chronic inflammatory and neurodegenerative disease of the central nervous system (CNS). It is considered the most common autoimmune demyelinating disease of the CNS. It affects mainly young adult females between 20-40 years of age. MS was previously considered a T-lymphocyte-disease, but now B lymphocytes appeared to have a critical role in MS's pathogenesis. Affected patients showed lower quality of life with an increased death rate than the general population. The treatment of MS is challenging, and many drugs have evolved primarily for the last 20-30 years. Since the introduction of interferons in 1993, there are more than sixteen disease-modifying therapies (DMTs) approved. These drugs have different pharmacologic forms like injections, oral forms, and intravenous infusion drugs. Each one has its benefits and drawbacks. Moreover, like any other patient, MS patient has other symptoms that are not covered by DMT and need symptomatic treatment. In this chapter, we attempt to present medications used to treat acute relapse, different DMTs, symptomatic treatment for different MS symptoms. Besides, we give attention to drugs under clinical trials.

Keywords: Acute Relapse, Disease-modifying Therapy (DMT), Multiple Sclerosis (MS), Symptomatic Treatment.

INTRODUCTION

Multiple sclerosis (MS) is a well-known chronic inflammatory and neurode-

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generative disease of the central nervous system (CNS). It is considered the most common autoimmune demyelinating disease of the CNS [1, 2]. MS affects mainly young adult females between 20-40 years of age [3]. The prevalence of MS varies with latitude, with an estimated global prevalence of 30.1 cases per 100,000 persons in 2016. The higher prevalence was found in North America, Western Europe, and Australia and lowest in eastern sub-Saharan Africa, central sub-Saharan Africa, and Oceania [4]. The precise etiology of the disease is not recognized. However, it is likely to develop in genetically susceptible individuals on exposure to various environmental factors [5]. MS is classified into four phenotypes: clinically isolated syndrome (CIS), relapsing-remitting (RR), primary progressive (PP), and secondary progressive (SP). Each type is further subcategorized to either active or non-active [6]. At disease presentation, 85% present with RRMS form, while 15% present with PPMS form. About 80% of patients with CIS who have typical brain lesions will develop MS during the follow-up. After 20 years, 80% of patients will develop SPMS [7]. RRMS presents with subacute onset of symptoms that may include optic neuritis, long-tract symptoms (weakness, numbness, paresthesias), impaired balance, brainstem dysfunction (internuclear ophthalmoplegia or nystagmus), transverse myelitis, or L'hermitte sign. PPMS present at a relatively older age (39-41 years), typically with a gradual progressive spastic paraparesis without sensory level [8, 9]. The pathogenesis of MS can be explained by self-reactive immune cells that break down the immune tolerance and reach the CNS, where they attack the myelin sheath. When reaching the CNS, these autoreactive lymphocytes start demyelination, axonal degeneration, synaptic loss, dying-back oligodendrogliopathy, tissue loss, and eventually astrogliosis [10, 11]. MS was previously considered a T-lymphocyte-disease, but now B lymphocytes have a critical role in MS's pathogenesis [12, 13]. The instant response to B-cell–depleting monoclonal antibodies suggests that antigen presentation and production of proinflammatory chemokines and cytokines by B lymphocytes (as contrasted to their antibody production role) may be more relevant to MS pathogenesis [14]. The discovery of the meningeal lymphoid follicle-like aggregates the possibility of intrathecal inflammation and may be responsible for disease progression [15]. Although the adaptive immune system drives the pathogenesis early in the disease, other mechanisms take the upper hand later. These disease processes are innate immune system, mitochondrial dysfunction, glutamate toxicity, and reduced compensatory ability. All these mechanisms lead to the accumulation of disability with advancing age [16]. MS patients showed lower levels of quality of life and an increased rate of death compared to the general population [17, 18]. The treatment of MS is challenging, and many drugs have evolved primarily for the last 20-30 years. Since the introduction of interferons in 1993, more than sixteen disease-modifying therapies (DMTs) have

been approved. These drugs have different pharmacologic forms like injections, oral forms, and intravenous infusion drugs. Each one has its benefits and drawbacks. Moreover, like any other patient, MS patient has other symptoms that are not covered by DMT and need symptomatic treatment. This chapter attempts to present medications used to treat acute relapse, different DMTs, symptomatic treatment for different MS symptoms, and besides, we give attention to drugs under clinical trials.

TREATMENT OF RELAPSES IN MULTIPLE SCLEROSIS

Intravenous Methylprednisolone

Treatment of relapses with intravenous methylprednisolone (IVMP) reduces post relapse disability by the mechanism of immunologic alterations, the reduction of B-lymphocytes count, and their availability at the inflammatory sites, which could result in a decreased number of immunoglobulin (Ig) G synthesizing cells in the CNS. This may lead to a reduction of the blood-brain barrier permeability [19]. The half-life of circulating MP is 1.5 hours, and the half-life of its metabolites is 4 hours. It reaches its peak concentration in 2 hours in plasma and 6 hours in CSF [20]. Daily IV dosage is 500-1000 mg and the administration period is 5-10 days. It is usually administered in 100-300 mL of 0.9% NaCl or 5-10% dextrose solution for at least 60 minutes and slower in patients with cardiac diseases. Maintaining oral therapy after IV administration does not provide benefits [21]. In optic neuritis study, administration of 1 g/day IV MP for three days, followed by 21 days of oral MP, is superior to oral MP administration alone [22]. Unresponsiveness to IVMP treatment can only be considered at least ten days after the end of administration [23]. The treatment in pregnant women can be applied in the 2nd and third trimesters of pregnancy but should not be given in the first trimester. The administration should be given after milking the postpartum lactating mother. Mothers can breastfeed 4 hours after the administration [24]. Adverse events (AEs) of steroids are hyperglycemia and glycosuria (5%), gastrointestinal intolerance and dyspepsia, insomnia (72%), followed by depressed mood (62%), metallic taste in the mouth (59%), headache (59%), anxiety (56%), and swelling of the body (52%), and infections are among the other adverse effects of steroids. It can very rarely cause aseptic femoral head necrosis and cataracts.

Adrenocorticotropic Hormone (ACTH)(Acthar® Gel)

Acthar gel was used a lot in the 1980s to treat acute relapses in MS but fell out of favor. Patients may refuse, be unable to use, or show nonresponse to conventional steroid treatment of multiple sclerosis (MS) exacerbation [25]. Adrenocorticotropic hormone (ACTH), one of several melanocortin peptides with

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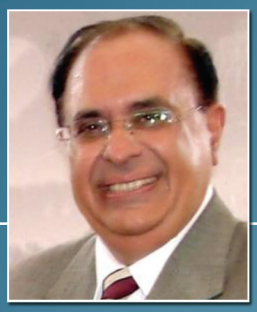

PROF. DR. ATTA-UR-RAHMAN, *FRS*

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.

DR. ZAREEN AMTUL

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.