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Editor:
Atta-ur-Rahman, *FRS*

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Frontiers in Clinical Drug Research - CNS and Neurological Disorders

Volume 4

Edited By

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CONTENTS

PREFACE

The book series ***Frontiers in Clinical Drug Research – CNS and Neurological Disorders*** contains the most noteworthy recent developments for the treatment of several neurological disorders. The volume 4 of this book series is a collection of well written cutting edge reviews contributed by some of the most prominent researchers in the field.

Multiple sclerosis (MS) is a potentially disabling disease of the central nervous system in which the immune system attacks the myelin and causes communication complications between the brain and the body. It affects some two million persons across the world. In chapter 1, Rigolio *et al*. present an excellent overview of the old and new cellular and molecular therapeutic approaches to fight MS neurodegenerative progression.

Alzheimer's disease (AD) is the most common age-related multifactorial neurodegenerative disease which is described as the failure of cognitive performance and behavioral capabilities and there is a desperate need for the treatment to prevent, stop or reverse this devastating disorder. The magnitude of the problem can be judged from the fact that of the 46.8 million people suffering from dementia worldwide, the majority belong to those suffering from AD and this number is expected to triple over the next 30 years. In chapter 2 Villegas *et al*. discuss several biomarkers for early detection, clinical trials under way on new drugs, and preclinical research involving different approaches to tackle Alzheimer's disease.

In chapter 3 Cavanagh & Krantic discuss two aspects of AD, hyperexcitability and neuroinflammation, which can be used for future therapeutic intervention. They also summarize the studies, which are related to hyperexcitability and neuroinflammation in the early phases of the disease.

Diabetic neuropathy (DN) is characterized by neurodegeneration associated with diabetes mellitus which belongs to the earliest and most frequent chronic diabetic complications. It may occur in clinical form or in subclinical form. High blood sugar affects nerve fibers throughout the body, but diabetic neuropathy most often damages nerves in the legs and feet. Vojtková *et al*. in chapter 4 present a comprehensive review about current possibilities and future perspectives in the management and treatment of diabetic neuropathy.

Migraine is a primary headache disorder characterized by moderate to severe recurrent headaches. Erdener & Dalkara in chapter 5 focus on the current and future therapeutic agents for acute and prophylactic migraine treatment and their mechanisms of action. In chapter 6, the Arsava and Dalkara present a review on developments in the treatment of acute ischemic stroke. They also discuss the recent advancements in the secondary prophylaxis of ischemic

stroke.

The 4th volume of the book series represents the results of a significant amount of work by eminent researchers in the field. I am grateful to the authors for these valuable contributions. I also wish to thank the excellent team of Bentham Science Publishers, especially Mr. Shehzad Naqvi (Senior Manager Publications), led by Mr. Mahmood Alam (Director Publications), who deserve our appreciation.

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CHAPTER 1

Multiple Sclerosis Drug Therapy: From the Classical Pharmaceutical Down to Cellular and Molecular Approach

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Abstract: Multiple Sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) affecting over 2.000.000 individuals around the world. Although MS etiopathogenesis is still not completely defined environmental factor exposure and genetic background are relevant in disease development. Moreover, MS shows heterogeneous onset and course so that different disease forms can be described which are all characterized by motor and/or sensory and even cognitive impairment.

Two steps in the disease progression can be described. First MS lesions are originated by the activated immune system which recognizes CNS myelin as a foreign element thus leading to the formation of demyelinated plaques that evolve into axonal damage and subsequent neurodegeneration over the time.

Since the beginning MS therapy has been focused on counteracting immune system action. Nevertheless, besides the immunosuppressive/immunomodulating drugs such as Glatiramer acetate, Beta-interferons and steroids, the advance in the comprehension of the immune-mediated mechanisms has sustained the development and use of molecular

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Atta-ur-Rahman (Ed.)

and cellular-focused approaches, *e.g.* monoclonal antibodies and stem cells.

At the same time very few weapons are specifically available for fighting MS neurodegenerative progression.

We report an overview on MS and both old and new therapeutic approaches to the disease.

Keywords: Alemtuzumab, Anti-Lingo-1 antibody, Daclizumab, Disease-modifying drugs, Ethiopathology, Helminthes, Histopathology, Immune system, Masinitib mesylate, Monoclonal antibodies, MOR103, Multiple Sclerosis, Ocrelizumab, Ofatumumab, Remyelination strategies, Rituximab, Secukinumab, Stem cells, Tabalumab, Tolerogenic vaccines, Vitamin D.

MULTIPLE SCLEROSIS

Over the past 100 years the advances in immunology and neurobiology have led us to the current definition of Multiple Sclerosis (MS) as a chronic inflammatory disease of the central nervous system (CNS) primarily triggered by the activation of immune system elements against myelin sheath components, which is subsequently followed by irreversible damage to axons and neurons leading to permanent disability. Until now, no single etiopathogenetic factor has been identified and MS is generally considered to be a complex multifactorial autoimmune disease depending on genetic predisposition and environmental factors.

MS is characterized by a dissemination of CNS lesions in time and space with heterogeneous signs and symptoms that usually indicate more than one lesion and that can be due to injury to any part of the neuraxis. Moreover MS clinical presentation and course are highly variable. Several disease types can be recognized: relapsing-remitting MS (RRMS), primary-progressive (PPMS), secondary-progressive (SPMS).

Although our current pathogenetic concepts might be too simple to define such a multifaceted disease, our current knowledge of the MS-related immunological mechanisms has made possible the clinical viability of various effective immunomodulating/immunosuppressive strategies. These are mainly aimed at

limiting/modifying the inflammation-related component of the disease so that the main part of the research activity and treatments has been focused on the RRMS form, while the MS symptoms are mainly managed by means of non-specific symptomatic therapies.

Epidemiology, Environmental Agents and Genetics

MS is the most frequently diagnosed neurological disease leading to non-traumatic disability among young adults, affecting more than 2 million individuals worldwide [1]. As with many other autoimmune diseases, the prevalence of MS is 2-3 times as high in women as in men and this ratio seems to have increased slightly over time, mainly in the polar latitude countries [2]. The incidence of MS has increased in various countries due both to the improvement in diagnostic tools and to the lengthening of patients' lives together with the improvement in hygiene conditions over the last century [3].

MS can affect individuals at any age with the first clinical signs occurring most frequently between 20 and 40 years of age although the disease can occur even in individuals over 50 years of age; pediatric MS has also been recognized and diagnostic criteria have recently been redefined [4, 5]. The prevalence of the disease has been shown to increase from the equator to the pole with important exceptions such as the Sardinian and the Inuit populations in the Mediterranean and Canada respectively. Moreover, the migration studies which have shown changes in the risk of MS susceptibility in individuals moving to different MS-risk areas before pubescence [6] and the fluctuations in the rates of MS patients in some areas such as the North Atlantic islands have suggested a strong interaction between genetically-based and environmental factors, *i.e.* viruses, vitamin D deficiency and other factors [1, 7].

Thanks to these epidemiological studies, a hygiene hypothesis has been put forward suggesting that the higher incidence of MS in industrialized countries is due to certain infections or inappropriate responses to certain substances [8]. This notion is supported by analogies of the geographical distribution of certain infections [9], and by the fact that, in developed countries, certain typical childhood diseases, such as measles or mononucleosis, are contracted at later

CHAPTER 2

Prospective Therapies for Alzheimer Disease: Biomarkers, Clinical Trials and Preclinical Research

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Abstract: Most of the 46.8 million people estimated in the year 2015 as living with dementia worldwide were attributed to have Alzheimer's disease (AD), with projections set to be almost tripled by 2050. Current drugs to treat AD are focused on ameliorating symptoms instead of treating its underlying causes, becoming only palliative. Consequently, treatments to prevent, stop or reverse this overwhelming disease are desperately needful. This Chapter takes a tour through clinical and pre-clinical studies from different approaches, ranging from those based on small molecules to immunotherapy. But first it also addresses the role of biomarkers in early diagnosis, which is necessary not only to properly recruit patients but also for an accurate assessment of efficiency and safety in clinical trials. Among other approaches, Aβ- immunotherapy has emerged as a promising tool for the treatment of AD. Whereas active immunotherapy, namely administering fragments of the Aβ-peptide, is currently in Phase II, passive immunotherapy, specifically administering antibodies against the Aβ-peptide, reached Phase III. Some of these Phase III trials failed probably because they were performed in patients with mild-to-moderate AD, a too advanced stage of the disease. Currently, different cohorts have been recruited for clinical trials:

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Atta-ur-Rahman (Ed.)

asymptomatic and very-mildly symptomatic carriers of autosomal-dominant AD mutations as well as symptomatic elderly patients with amyloid positive PET. More studies are needed, but we are getting closer to find a disease-modifying drug to cure this devastating disease.

Keywords: AD biomarkers, AD imaging, Alzheimer's disease, Amyloid-β, APOE, APP, Immunotherapy, New therapies, PSEN, Vaccine.

I. INTRODUCTION

I.1. Background

On November 1906, Alois Alzheimer reported an oral communication "On a peculiar severe disease of the cerebral cortex" to the 37th Meeting of South-West German Psychiatrists in Tubingen. He described the pathology of a 50-year-old woman whom he had followed since her admission for memory loss, disorientation, hallucinations, and dementia, until her death 5 years later. His report noted particular features in the brain histology: a dramatic reduction in the number of cortical cells as well as distinctive extracellular plaques and intracellular neurofibrillary tangles (NFTs). Little interest was aroused despite an enthusiastic response from Emil Kraepelin, who included the term "Alzheimer's disease" (AD) in the 8th edition of his text "Psychiatrie" in 1910.

The term "amyloid", stemmed from the Latin word "amylym", was first referred in the XIX century as the substances featuring a positive staining for starch. Just after cellulose was known to change from brown to blue upon iodine-sulfuric acid reaction, positive small round deposits were described in the nervous system. It was not until 1984 when Glenner and Wong first reported a 4 kDa peptide as the main component of cerebrovascular amyloids associated to AD [1]. Subsequently, the sequencing of the A4 peptide ("A" stands for "amyloid" and "4" refers to the Mw) from the core of amyloid plaques dissected from AD and old-age DS (Down Syndrome) individuals allowed the localization of the gene coding its precursor (APP, Amyloid Precursor Protein), a cell-surface receptor, on human chromosome 21 [2]. Nowadays the A4 peptide is known as the Aβ peptide because it aggregates featuring β-sheet secondary structure [3]. The intracellular NFTs turned out to be constituted by aberrant forms (typically hyperphosphorylated and

fragmented) of tau, a microtubule-associated protein [4]. In contrast to Aβ-peptide, abnormal tau metabolism is also associated to other neurodegenerative diseases, collectively referred to as tauopathies [5]. Both, the Aβ-peptide and abnormal tau, are known to trigger oxidative stress and inflammatory responses during AD progression.

I.2. Alzheimer's Disease and the Need for New Drugs

Most of the 46.8 million people estimated in the year 2015 as living with dementia worldwide were attributed to have AD, with projections set to 74.7 million by 2030 and 131.5 million by 2050 [6]. AD begins with trouble remembering some daily events and evolves into a progressive dysfunction in orientation in time and space and, finally, into a general deficit in motor functions. Because the neurodegenerative process may extend for over a decade, the associated dementia causes a long suffering to both patients and their caregivers. In consonance, the economic impact is huge, with an US$818 billion worldwide estimated in 2015 [6]. This cost comprises social care provided by community professionals, informal care provided mostly by relatives and medical care. Because there are no drugs that can halt its progression, treatments to prevent, stop or reverse this overwhelming disease are desperately needful.

Currently, two types of drugs are approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the palliation of AD symptoms: those acting on the cholinergic system and one acting on the glutamatergic system. Because the death of cholinergic neurons is the main output of the pathology, increasing the levels of acetylcholine partially compensates for the loss of this neurotransmitter [7]. The cholinesterase inhibitors donepezil, galantamine, rivastigmine and tacrine are used for this purpose. On the other hand, it is known that glutamate is increased in AD patients, as well as in other neurodegenerative diseases, and that this unbalance leads to cell death. Memantine, an antagonist of N-methyl-D-aspartate (NMDA) receptors, a subtype of ionotropic glutamate receptors, is thought to have a neuroprotective effect [8]. However, these drugs only have palliative benefit during some stages and are very individual dependent.

CHAPTER 3

At the Crossroad between Neuronal Hyperexcitability and Neuroinflammation: New Therapeutic Opportunities for Alzheimer's Disease?

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Abstract: Alzheimer's disease (AD) is a multi-faceted neurodegenerative disease. Clinically available treatments, such as cholinesterase inhibitors, are based mainly on the cholinergic hypothesis of AD. These treatments, as well as those targeting the NMDA type of glutamate receptors all provide only a limited therapeutic benefit. The field of AD research has also shifted focus to develop intervention strategies that prevent overt symptoms, such as amyloid plaque deposition and memory loss, in agreement with the more recent amyloid hypothesis of AD. However, to date, all amyloid-directed therapeutics for the treatment of AD have failed, suggesting that additional factors may be involved in the etiology of the disease and mobilizing the

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Atta-ur-Rahman (Ed.)

search for additional drug targets. By studying the early stages of AD, candidate drug targets (*e.g.* cytokines or neuronal network activity) have been identified and are now at advanced stages of preclinical development. Throughout this chapter we will focus on two aspects of AD that have garnered widespread attention with respect to future therapeutic intervention strategies. First, a common feature of both mouse models of AD and patients with the disease is hyperexcitability at the level of the synapse as well as neuronal networks. New research is starting to uncover the causes of this hyperexcitability and which cell types are vulnerable, thus, providing attractive therapeutic targets. Second, AD brains are affected by neuroinflammation-like alterations at early stages, which turn into overt neuroinflammation at the late stages. Reducing this activity by targeting the proinflammatory cytokine, tumor necrosis factor-α (TNFα), is thought to be a promising strategy to treat AD. Furthermore, given the cross-talk between the nervous system and the immune system, we hypothesize that the hyperexcitability and progressive induction of neuroinflammation may be related. Here, we summarize studies in both animal models of AD and AD patients related to hyperexcitability and neuroinflammation in the early stages of the disease. Finally, we propose that a combination treatment targeting these factors in addition to the amyloid burden would be a possible way to target more facets of AD.

Keywords: Alzheimer's disease, Amyloid, Hyperexcitability, Inflammation, Intervention, Prodromal, Synaptic, TNFα.

INTRODUCTION

Alzheimer's disease (AD) and related dementias affect an estimated *44 million* people worldwide [1], a number that will only grow with the aging population unless new therapies are developed. AD develops insidiously over decades and can remain undiagnosed for years until the manifestation of overt symptoms. These overt symptoms include loss of cognitive functions that interfere with the individuals' ability to perform daily tasks, trouble remembering recent events and eventually total memory loss, as well as a host of other symptoms such as agitation, paranoia, sleep disturbances and aggression. The hallmark histopathological features of AD include extracellular, senile plaques composed of amyloid-beta (Aβ), intracellular tangles composed of hyperphosphorylated tau and neuronal loss [2]. However, these features represent only a fraction of this multi-faceted disease and research in animal models is uncovering additional hypotheses for possible causes of AD.

The purpose of this chapter is to summarize and provide new insights into the treatment of AD. We will focus on two aspects of AD that research suggests are particularly important to the pathogenesis of the disease namely, neuroinflammation and synaptic function, as well as how they are related. We propose that the treatment of AD will ultimately require a multi-targeted, stage-specific approach to address multiple facets of the disease.

1. BACKGROUND ON AD

The prevailing theory on the cause of AD is the amyloid cascade hypothesis, which states that the overproduction of Aβ from the amyloid precursor protein (APP) initiates a series of events, including synaptic dysfunction, microglial and astrocytic activation and hyperphosphorylation of tau, which culminates in widespread neuronal death [2]. Although this hypothesis is supported by strong genetic evidence, which will be described below, all amyloid-directed therapeutics tested to date have failed in clinical trials. In addition, this hypothesis has been challenged by findings of amyloid plaques in cognitively healthy individuals upon post-mortem analysis [3]. However, these findings may reflect the ability of some to cope better with AD pathology than others [3]. Although it is hard to discount the contribution of Aβ to the disease, the search is underway for additional drug targets and contributors to AD pathology.

1.1. APP Processing

Aβ is a 4kDa protein produced through the sequential cleavage of APP, which is a transmembrane protein. APP can be processed in one of two ways, either along the amyloidogenic pathway, which generates Aβ or the non-amyloidogenic pathway. The amyloidogenic pathway involves an initial cleavage step by β-secretase or β-site APP cleaving enzyme 1 (BACE1) to produce the β-C-terminal fragment (βCTF), which is retained in the membrane and the secreted APP-β fragment (sAPPβ). βCTF then undergoes a second cleavage step by γ-secretase to liberate Aβ and the APP intracellular domain (AICD) peptide. Along the non-amyloidogenic pathway, the first cleavage step is by α-secretase, which produces the α-C-terminal fragment (αCTF) and the secreted APP-α (sAPPα) fragment. The second cleavage step along this pathway is also by γ-secretase, which cleaves α-

CHAPTER 4

Treatment of Diabetic Neuropathy – Current Possibilities and Perspectives

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Abstract: Diabetic neuropathy (DN), characterized by nerve damage associated with diabetes mellitus, belongs among the earliest and most frequent chronic diabetic complications. It may occur in clinical form (as peripheral sensory/motor, autonomic, proximal, painful or focal) or in subclinical form detectable just by sensitive diagnostic methods. The etiology of DN is complex and not fully understood, untill now. Long-term hyperglycemia triggers a variety of interacting pathways such as production of advanced glycation end products (AGEs), products of oxidative stress and polyol pathway, protein kinase C activation, decrease activity of Na^+K^+ATP-ase, changed concentration of neural growth factor and production of proinflammatory cytokines. These pathomechanisms may target directly on nerve cells or on endothelial cells causing the microangiopathy of vasa nervorum.

According to multicentric studies, duration and poor compensation of diabetes are the principal risk factors associated with the development of chronic diabetic complications, so the basis for the management is to maintain adequate metabolic compensation. Intensified insulin regimen is the most effective in the treatment of patients with type 1 diabetes. In patients with type 2 diabetes, administration of selected peroral antidiabetics or insulin therapy is considered. Physical activity, lifestyle and dietary management also contribute to euglycemia. Currently used management of DN includes supportive (alpha-lipoic acid, vitamins, antioxidants) and symptomatic treatment (painkillers, beta blockers, magnetotherapy). Other therapeutic possibilities are experimental so far. These drugs interfere with the pathophysiological processes and few of them have been shown to be beneficial in clinical studies

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Atta-ur-Rahman (Ed.)

(inhibitors of aldose reductase, selective inhibitor of protein kinase C beta, C peptide substitution), however, the effect of other medicines seems to be controversial (vascular endothelial growth factor, erythropoietin). This chapter brings comprehensive review about current possibilities and future perspectives in the management of diabetic neuropathy.

Keywords: Actovegin, Aldose-reductase inhibitors, Alpha-lipoic acid, Angiotensin converting enzyme inhibitors, Anti-inflammatory drugs, Antioxidants, Chronic complications, C-peptide, Diabetes compensation, Diabetes mellitus, Diabetic neuropathy, Electrical nerve stimulation, Epigenetic modifications, Erythropoietin, Experimental studies, Growth factors, Kinin B_1 receptor, Management, Magnetic field therapy, Neurotrophic factors, Pain relief, Ruboxistaurin, Spinal cord stimulation, Vascular endothelial growth factor, Vitamins.

INTRODUCTION

Diabetes mellitus represents a chronic metabolic disease of heterogeneous etiology with hyperglycemia as the main symptom caused by insufficient action of insulin because of its absolute or relative deficiency and is accompanied by the disorder of metabolism of sugars, lipids, proteins, water and minerals. Considering dramatically the increasing incidence of diabetes worldwide, it is becoming a pandemic with a huge impact on the individual and on the whole society, as well. Diabetes can negatively influence the quality of life, especially by the presence of chronic diabetic complications. Among the earliest diabetic complications belongs diabetic neuropathy, characterized as a disorder of the peripheral nervous system associated with diabetes mellitus. According to the type of affected nerves, it can be divided into sensory, motor, autonomic or mixed neuropathy. Concerning the still earlier onset of diabetes, diabetic neuropathy can be found also in childhood and adolescence, even just few years after type 1 diabetes onset. In its complex etiopathogenesis, the main risk factor is long-lasting hyperglycemia, the impact of which is enhanced by poor compensation and longer duration of diabetes, together with genetic predisposition and probably also immunologic, epigenetic or other factors. Hyperglycemia may trigger a variety of processes, such as non-enzymatic glycation, oxidative stress, polyol pathway,

activation of protein kinase C, proinflammatory cytokines, changed concentration of neural growth factor or decrease activity of Na^+K^+ATP-ase. These processes may either directly alter the structure and function of neurocytes or may indirectly damage the blood supply of neurons through disorder of endothelial cells.

The management of diabetic neuropathy is complex. The first step involves the maintenance of adequate diabetes compensation – to control glycemia, lipid profile and blood pressure. In addition to insulin therapy (or per oral antidiabetic drugs), lifestyle modification, dietary management and adequate physical activity significantly contribute to euglycemia. Current treatment of diabetic neuropathy includes alpha-lipoic acid and vitamins (C, E and group B). Symptomatic treatment is aimed to relieve pain and to relieve possible symptoms of autonomic neuropathy (such as tachycardia, hypotension, gastroparesis and bladder atonia). Other possibilities are mostly experimental, and interfere with the mentioned pathogenic pathways. Results of some clinical studies are very promising and may represent possible options in complex management of diabetic neuropathy.

DIABETES MELLITUS

Diabetes mellitus represents a chronic metabolic disease of heterogeneous etiology with hyperglycemia as the main symptom caused by insufficient action of insulin because of its absolute or relative deficiency. Diabetes is accompanied by disorders of metabolism of sugars, lipids, proteins, water and minerals.

According to American Diabetes Association [1] the classification of diabetes mellitus is:

I. Type 1 diabetes mellitus (T1D)
II. Type 2 diabetes mellitus (T2D)
III. Specific types of diabetes
   Genetic defects of beta cells, Genetic defects of insulin action, Diseases of exocrine pancreas, Endocrinopathies, Diabetes induced by drugs and chemicals, Infections, Uncommon forms of immune-mediated diabetes, Other genetic syndromes sometimes associated with diabetes
IV. Gestational diabetes mellitus

CHAPTER 5

The Now and Tomorrow of Migraine Treatments

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Abstract: The last few decades have witnessed a major progress in migraine treatment based on novel clinical findings as well as advanced pathophysiological understanding of the disease. Studies focusing on the activation of trigeminovascular system during migraine attacks complemented by identification of several genes related to migraine susceptibility have elaborated the role of dural neurogenic inflammation, nociceptive sensitization mechanisms and cortical spreading depression in migraine pathophysiology. Triptans and CGRP antagonists have emerged as novel migraine-specific agents for acute attack treatment although clinical use of CGRP antagonists is hampered by their side effects. Several unrelated classes of drugs ranging from beta-blockers to antiepileptics have been identified to be effective for migraine prophylaxis. A wide variety of novel targets including CGRP, glutamate receptors, nitric oxide synthase are in drug development pipeline for both acute as well as prophylactic treatment. Availability of a wide range of experimental and human models of migraine is promising in facilitating this progress. This chapter will focus on the current and future therapeutic agents for acute and prophylactic migraine treatment and their mechanisms of action.

Keywords: Antiepileptics, CGRP antagonists, Drug treatment, Headache, Migraine, Neurogenic inflammation, NSAIDs, Spreading depression, Trigeminovascular system, Triptans.

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Atta-ur-Rahman (Ed.)

INTRODUCTION

Headache is a common symptom confronted not only by neurologists but by all physicians. Migraine is a common form of primary headaches, affecting about 15% of the World population [1]. Migraine attacks are typically characterized with unilateral, throbbing and disabling headache episodes lasting for 4-72 hours and, are generally associated with nausea, vomiting, photophobia and phonophobia. In 20-30% of migraineurs, transient neurological symptoms, called *aura* gradually spread over 5 minutes and are accompanied or followed by headache within typically 15-60 minutes. Aura symptoms include visual disturbances (scintillating scotoma, blurring, homonymous visual field defects), migrating paresthesia and numbness in the face or extremities and, occasionally, speech disturbances as well as motor or brain stem dysfunctions. Today's physicians are fortunate with many therapeutic options available for treating migraine headaches or reducing the attack frequency compared to 30-40 years ago. However, success rate is still not satisfactory and drugs used have unwanted side effects. Overcoming these limitations has been the subject of many recent preclinical and clinical research efforts. Here, we will review the currently used and emerging migraine therapies.

PATHOPHYSIOLOGICAL OVERVIEW

It is generally agreed that migraine attacks are initiated by transient disturbances in the brain parenchyma and that the first division of the trigeminal cranial nerve along with the upper cervical nerves, which innervate the meninges and cerebral blood vessels mediate the nociceptive impulses to generate headache. Consequently, a detailed understanding of the migraine pathophysiology encompassing multifaceted events in the brain parenchyma, meninges and trigeminovascular system (TVS) is needed for developing better therapies (Fig. **1**). Fortunately, research on a wide range of animal models as well as surgical, physiological and neuroimaging studies on human subjects have proved that they could be instrumental in identification of the pathophysiological pathways and novel drug targets.

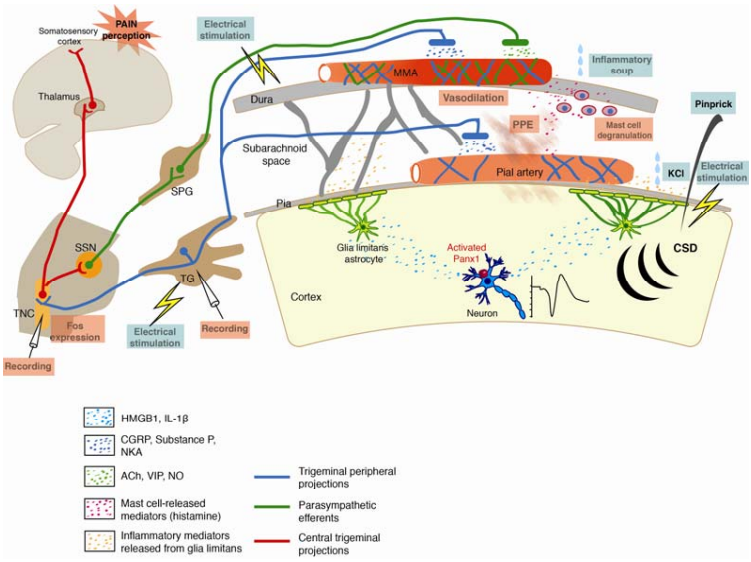

Fig. (1). Activation of trigeminovascular system by a parenchymal inflammatory signaling pathway leads to headache. Trigeminal ganglion (TG) neuron processes peripherally terminate over the pial and dural vessels, whereas central processes synapse in TNC. Second-order TNC neurons project to thalamus. Meanwhile, collaterals activate the parasympathetic superior salivatory nucleus (SSN), which innervate dural vessels via spehenopalatine ganglion (SPG) route. TVS activation leads to release of several mediators from perivascular nerve endings, hence, induce dural vasodilatation, mast cell degranulation and extravasation of plasma proteins. The TVS can experimentally be activated by chemical or electrical stimulation of the dura or trigeminal ganglion as well as by CSD. CSD initiates a parenchymal inflammatory signaling cascade by opening of neuronal pannexin-1 (Panx1) channels and release of HMGB1 and IL-1β. This response leads to activation of trigeminal nerve fibers around pial blood vessels. Experimentally, nociceptor activation can be demonstrated by electrical recordings from TG or TNC or by immunolabeling of TNC for Fos. Dural vessel dilatation, mast cell degranulation and protein extravasation can also mark TVS activation. [Reproduced, with permission from [12]].

Activation of the TVS causes release of several vasodilatory peptides like calcitonin gene related peptide (CGRP), pituitary adenylate cyclase-activating peptide (PACAP), substance-P and vasoactive intestinal polypeptide (VIP) from nociceptive nerve endings innervating the dura [2]. These mediators lead to discharge of additional vasodilators like histamine from dural mast cells. The vasoactive mediators induce plasma protein extravasation from dural vessels in addition to vasodilation [3 - 5]. Central projections of trigeminal and cervical nociceptive afferents terminate on the trigeminal nucleus caudalis (TNC), which extends from lower medulla oblongata to upper cervical spinal cord, forming the

CHAPTER 6

The Now and Tomorrow of Ischemic Stroke Treatment

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Abstract: The last decade has witnessed a number of major developments in the field of stroke. A major breakthrough in the treatment of ischemic stroke was attained by the demonstration of improved functional outcomes with intravenous tissue plasminogen activator therapy in the hyperacute period. Recent efforts of pre-hospital thrombolysis facilitated by the use of specialized stroke ambulance systems and newer generation thrombolytics provide promising results in terms of optimizing the benefit obtained from intravenous thrombolysis. These advances, together with successful results observed by endovascular recanalization, especially by the use of thrombectomy devices, unambiguously demonstrate that the penumbra concept (presence of a salvageable ischemic brain tissue) is valid. Despite these encouraging developments, other approaches like neuro-glial protection or restoration have not been so successful in patients with acute ischemic stroke. Nonetheless, there is still hope for these therapies, especially if clinical and radiological algorithms are developed for appropriate patient selection and the recanalization is supplemented by measures aiming neuroprotection and restoration of blood flow not only at the arterial but also microcirculatory level. As for secondary prophylaxis of ischemic stroke, the availability of new anti-platelet and anti-coagulant agents combined with the progress attained in risk factor control has led to an impressively significant reduction in stroke related mortality and morbidity over the last decades.

Keywords: Anticoagulants, Antiplatelet agents, Drug treatment, Endovascular recanalization, Ischemic stroke, Microcirculation, Neuroprotection, Penumbra,

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Atta-ur-Rahman (Ed.)

Thrombolytics.

ADVANCES IN TREATMENT OF ACUTE ISCHEMIC STROKE

Over the years numerous therapeutic approaches have been developed and tested in experimental models of cerebral ischemia and human stroke, with the ultimate goals of establishing recanalization/reperfusion, neuro-glial protection and prevention of secondary complications.

Recanalization/Reperfusion

A major breakthrough in acute ischemic stroke treatment was achieved in 1995 by the publication of the results of the National Institute of Neurological Disorders and Stroke (NINDS) recombinant tissue plasminogen activator (t-PA) study [1]. The randomized trial assessed the efficacy of intravenous t-PA against placebo treatment administered within 3 hours of symptom onset in ischemic stroke patients. Patients receiving intravenous t-PA at a dose of 0.9 mg/kg were more likely to harbor a favorable neurological outcome at 3-month follow-up in comparison to patients receiving placebo; specifically, the proportion of patients achieving a modified Rankin scale (mRS) of 0 to 1 was 42% in the t-PA arm and 27% in the placebo arm (absolute benefit ~15%, number needed to treat ~7, p=0.019) (Table **1**). This benefit of intravenous t-PA treatment was observed despite an approximately tenfold increase in the rate of intracerebral hemorrhage. The findings of the study were replicated when the data was pooled together with those of other t-PA trials [2]. The analysis showed a statistically significant absolute benefit of 12% for mRS of 0-1, and 8% for mRS of 0-2 at 3 months and, 8% for mRS of 0-2 in favor of t-PA (Table **1**). These publications consolidated the position of intravenous t-PA treatment as the first worldwide accepted and approved treatment strategy for acute ischemic stroke. As an additional important observation, the pooled analysis highlighted the importance of the ‘time is brain’ concept, by showing that the benefit obtained by intravenous thrombolysis being highest when the treatment was administered within 90 minutes of symptom onset. The efficacy persisted, but gradually declined and crossed the line of insignificance at 4.5 hours after symptom onset. Due to the hints of a potential efficacy between 3 and 4.5 hours after symptom onset, t-PA treatment was

compared against placebo specifically within this time window in the ECASS-III trial [3]. Of the patients receiving intravenous thrombolysis, 52% achieved a mRS of 0-1, whereas the corresponding figure was 45% in the placebo arm (absolute benefit 7%; number needed to treat ~14) (Table **1**). Based on these findings and replication of the trial data in the real-world experience [4] as well as in meta-analyses [5], intravenous t-PA treatment is currently considered as the standard of care in ischemic stroke patients who can be treated within 3 hours of symptom onset, unless there is a contraindication for the thrombolytic agent [6]. On the other hand, the use of t-PA for acute ischemic stroke within the 3-4.5 hour time window, although being recommended by major guidelines and approved by the European Medicinal Agency, is still not approved by the FDA.

Despite the proven efficacy of intravenous t-PA in acute ischemic stroke care, only 4-7% of ischemic stroke patients actually receive the treatment, primarily due to late admissions to the hospital after the therapeutic window is closed [7, 8]. More importantly, the treatment can be initiated within 90 minutes of symptom onset– the golden period with the maximum benefit obtained by treatment – in only a minority of patients [9]. Therefore, a number of strategies have been developed in order to increase the rates of t-PA administration to eligible patients. Telemedicine is one of them by which rural hospitals or centers without stroke neurologists available on site can consult patients for their eligibility for intravenous thrombolysis. They can even apply the so-called 'drip and ship' procedure in which t-PA treatment is initiated and the patient is transferred to a stroke center thereafter. The use of telemedicine and teleradiology systems has been shown to increase t-PA administration rates and decrease the onset-to-treatment time [6, 10]. In addition, by establishing strategies that promote population awareness, rapid transport and in-hospital infrastructure as well as organization, the delay between emergency department admission and treatment initiation could be cut down below 20 minutes [11]. However, recent studies have highlighted the fact that there is still room for improvement in optimizing treatment times by novel pre-hospital treatment strategies. These strategies, which probably will become an inherent part of future stroke care, make use of ambulance systems which include all the essentials for initiating on-site thrombolytic treatment: primarily a computed tomography mounted into the

SUBJECT INDEX

D

E

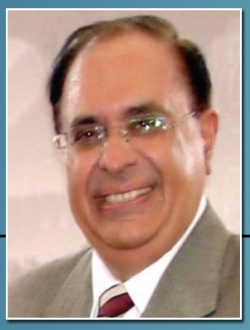
K

L

M

N

R



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

Atta-ur-Rahman, Ph.D. in organic chemistry from Cambridge University (1968), has 1020 international publications in several fields of organic chemistry including 727 research publications, 37 international patents, 68 chapters in books and 188 books published largely by major U.S. and European presses. He is the Editor-in-Chief of eight European Chemistry journals. He is Editor of the world's leading encyclopedic series of volumes on natural products "Studies in Natural Product Chemistry" 48 volumes of which have been published under his Editorship by Elsevier during the last two decades.

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