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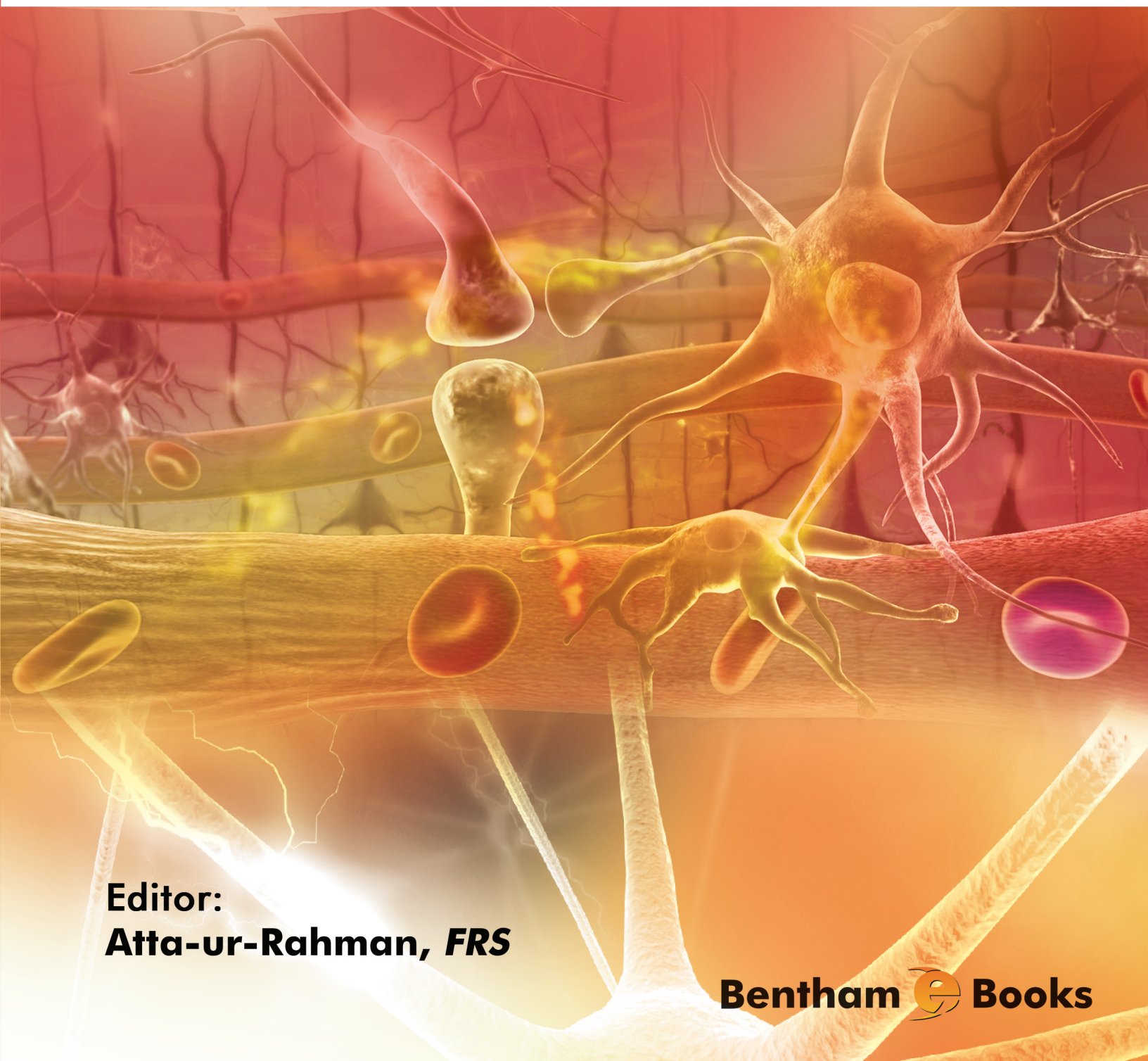

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Frontiers in Clinical Drug Research-Central Nervous System *(Volume 2)*

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Frontiers in Clinical Drug Research – Central Nervous System

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CONTENTS

PREFACE

The second volume of the eBook series entitled: "***Frontiers in Clinical Drug Research – Central Nervous System***" comprises five chapters in cutting edge fields. In the first chapter, Micheli *et al.* highlight the potential of nucleic acids as drugs for neurodegenerative diseases. Till date, various types of nucleic acid-based therapeutics have been proposed. This chapter demonstrates the rationale and current status of nucleic acid-based strategies for treating Huntington's disease and Parkinson's disease.

In the second chapter, Marcos Arturo Martínez Banaclocha discusses the current pharmacological interventions available for treating neurodegenerative diseases and brain aging. The author highlights the role of oxidised proteins at the cysteine residues in some neurodegenerative diseases and in aging.

Kazuo Abe focuses on non-motor symptoms in Parkinson's disease along with the pharmacological therapies to tackle the disease in the third chapter. In the fourth chapter, Anderson and Maes discuss melatonin interactions with the a7nAChR. In the last chapter of this eBook, Trevor R. Norman discusses another important disease of the Central Nervous System i.e. Major Depressive Disorder. The author highlights the pharmacological properties of some novel drugs and evaluates their efficacy critically.

I would like to thank all the contributors for their work and cooperation and would also like to appreciate all the technical staff of Bentham Science Publishers, especially, Mr. Mahmood Alam (Director Publications), Mr. Shehzad Naqvi (Senior Manager Publications) and Dr. Faryal Sami (Assistant Manager Publications) for their hard work and dedication.

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CHAPTER 1

Nucleic Acids as Drugs for Neurodegenerative Diseases

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Abstract: The development of nucleic acid-based therapeutics has recently aroused an increasing interest due to the great promise they hold for the treatment of a wide range of both inherited and acquired disorders. A prominent part in this field is played by neurodegenerative diseases, for which therapeutic interventions are currently limited to palliative and symptomatic treatment. Advances in the elucidation of the molecular mechanisms involved in these disorders provide the basis for developing nucleic acid-based treatment strategies able to address the molecular cause of the disease.

Several types of nucleic acid-based therapeutics have been proposed. All those therapeutics may be grouped into two main classes, *i.e.*, protein coding nucleic acids (DNA molecules) and regulatory nucleic acids (DNA or RNA molecules). The use of nucleic acids belonging to the first class is aimed at providing the relevant cells with a protein that either permits to rescue a missing function or supplies a new function able to counteract or alleviate the disease. Regulatory nucleic acids are used in order to counteract the harmful effects of a specific gene in the relevant cells. They include several types of molecules that allow virtually any step of gene expression to be controlled. Regulation at transcriptional and post-transcriptional levels can be achieved by the means of oligonucleotides, catalytic nucleic acids, siRNAs and antisense RNAs, while protein synthesis and protein function can be inhibited by siRNAs and aptamers or decoys, respectively.

The delivery of genes coding for neurotrophic factors as neuroprotective/ neurorestorative agents is a favored strategy for the treatment of neurodegenerative diseases, but a number of alternative strategies have also been proposed, such as the use of aromatic-L-amino decarboxylase (AADC) encoding gene for Parkinson's disease. More recently, advances in gene silencing technology have led to the evaluation of strategies aimed at selectively interfering with the pathogenetic mechanisms underlying disease phenotype, as in the case of Huntington's disease where RNA interference technology could provide a tool to target the mutant *HTT* allele.

A prerequisite for the successful clinical application of nucleic acid-based therapeutics to the treatment of neurodegenerative diseases is the availability of safe and efficient

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systems for nucleic acid delivery to the central nervous system, or better to the relevant neuronal subpopulations depending on the specific disease. A few viral vectors, those based on the adeno-associated virus or lentiviruses in particular, have shown promise as neuron-targeted nucleic acid carriers and the clinical trials undertaken to date have employed viral vectors almost exclusively. However, viral vectors have several drawbacks, such as those resulting from a non-complete safety, that significantly limit their widespread clinical use. Consequently, a great deal of efforts to develop non-viral vectors for nucleic acid delivery to the central nervous system has been made in the recent years. Non-viral vectors offer several advantages including improved safety profiles, lower production costs and ability to target specific neuronal subpopulations, but their delivery efficiency has to be improved in order to thoroughly realize their potential in clinical settings.

This chapter illustrates the rationale and current status of nucleic acid-based strategies for the treatment of two neurodegenerative movement disorders, Huntington's disease and Parkinson's disease.

Keywords: CNS-targeted nucleic acid delivery, Huntington's disease, movement disorders, neurodegenerative diseases, nucleic acid therapeutics, Parkinson's disease.

INTRODUCTION

Neurodegenerative diseases are a broad spectrum of central nervous system (CNS) disorders that are characterized by a chronic and progressive course and share a common hallmark consisting of the selective death of specific neuronal populations. The clinical manifestation of each neurodegenerative disease depends on the specific type of neurons that is involved. These disorders include both inherited diseases caused by single gene mutations (*e.g.,* Huntington's disease and several spinocerebellar ataxias) and common diseases of more complex origin (*e.g.,* Alzheimer's disease and Parkinson's disease).

Common age-related neurodegenerative diseases, along with cerebrovascular disorders, are currently among the leading causes of death and morbidity in Western countries and their prevalence is destinated to further rise as a consequence of average lifespan increase. This type of diseases exerts a growing impact from the societal and economic point of view, which makes the development of strategies for early detection as well as effective and safe treatments more important than ever.

Notwithstanding the significant advance made in recent years towards the elucidation of the pathogenic mechanisms underlying these various neurological disorders, no cures currently exist and therapeutic interventions are still limited to

palliative and symptomatic treatment. Therefore, much effort is being made to develop innovative therapeutic strategies and among these, nucleic acid-based strategies may have the potential for substantial advancements.

Nucleic acid-based therapeutic strategies, collectively known as gene therapy, refer to the delivery of nucleic acid molecules to target cell populations in order to achieve either the over-expression of a therapeutic gene, or inhibit the expression of an endogenous harmful gene, or even restore the function of a defective gene [1].

It was around the 1970s when the idea to deliver a therapeutic gene to treat human diseases came out [2] and the first foreseen application was the treatment of recessively inherited diseases by delivering a wild type copy of the defective gene responsible for the disease. Since then, the potential of gene therapy approach has been considerably increased by the development of novel kinds of therapeutic nucleic acids. Moreover, the range of candidate diseases for this treatment modality has expanded beyond that of inherited diseases to include more common diseases, such as cardiovascular disorders, cancer and degenerative disorders of CNS.

Two main nucleic acid-based approaches, “gene addition” and targeted inhibition of gene expression, are currently investigated for the treatment of neurodegenerative diseases. The earliest attempts at neurodegenerative disease gene therapy focused on the “gene addition” approach. Independent of the actual cause of neuron depletion, a therapeutic goal common to most neurodegenerative diseases is to preserve the viability and function of the residual neurons. Delivery of genes coding for neurotrophic factors as neuroprotective/neurorestorative agents is therefore an intensely investigated strategy. Further candidate therapeutic genes are chosen for each specific disease on the basis of available knowledge about the disease causing mutation or the pathogenetic mechanism underlying the disease.

More recently, advances in gene silencing technology have led to the evaluation of strategies aimed at selectively interfering with the pathogenetic mechanisms underlying disease phenotype. These strategies are applied to the targeting of gain-of-function mutant alleles in dominantly inherited diseases as well as genes known to contribute to the phenotype of more complex diseases.

This chapter illustrates the rationale and current status of nucleic acid-based strategies for the treatment of two neurodegenerative movement disorders, Huntington’s disease and Parkinson’s disease.

CHAPTER 2

Cellular Cysteine Network (CYSTEINET): Pharmacological Intervention in Brain Aging and Neurodegenerative Diseases

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Abstract: Reactive species have been regarded as by-products of cellular metabolism that cause oxidative damage contributing to aging, cancer and neurodegenerative diseases. However, accumulated evidence support the notion that reactive species mediate intracellular signals that regulate physiological functions including posttranslational protein modifications with important functional implications. Cysteine thiol groups of proteins are particularly susceptible to oxidative modifications by oxygen, nitrogen and sulfur species and they can be oxidized to several different products, including disulfide, sulfenic acid, sulfinic acid, sulfonic acid, S-nitrosothiols and S-glutathione, which have critical roles in cellular redox homeostasis. Since there are many cysteine-bearing proteins and cysteine-dependent enzymes susceptible to oxidative modifications that may contribute to cellular function and dysfunction, this chapter reviews the role of oxidative-changed proteins at cysteine residues in aging and some frequent neurodegenerative diseases. The concept of a cellular cysteine network (CYSTEINET) is advanced as a functional and structural matrix of interconnected proteins that in conjunction with reactive species and glutathione can regulate the cellular bioenergetic metabolism, the redox homeostasis, and the cellular survival. This network may represent an ancestral down-top system composed by a complex matrix of proteins with very different cellular functions, but bearing the same regulatory thiol radical. In this context and based on scientific evidences, current therapeutic and potential mechanism of action of some particular thiol bearing substances are revised.

Keywords: Acetylcysteine, aging, Alzheimer, cysteine, cysteinet, free radical, glutathione, hydrogen sulfide, mitochondria, neurodegeneration, nitric oxide, oxygen, Parkinson, reactive species, redox homeostasis, thiol.

INTRODUCTION

Normal cell metabolism generates oxygen, nitrogen and sulfur reactive species (ROS, RNS, and RSS respectively) that are finely controlled under physiological conditions. The disturbance of this cellular exquisite control results in oxidative

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stress that causes damage on all types of cellular macromolecules. If this oxidative stress is prolonged over time and antioxidant mechanisms become insufficient, the cellular damage may result in aging and a range of human diseases including cancer. At physiological conditions, reactive species can function not only as intracellular second messengers with regulatory roles in many cellular metabolic processes, but also as an ancestral biochemical network that control cellular survival, regeneration and death. An example of this class of bio-chemical matrix is reviewed and proposed in this chapter, which is named the cellular cysteine network (CYSTEINET). This cellular network is based on the finding that thiol groups of the amino acid cysteine are distributed through the majority of the proteins that have key roles in metabolic as well as structural functions in cells. In this chapter I elaborate the hypothesis that brain aging and age-related neurodegenerative diseases can be linked by oxidative modification of cysteine residues in a wide range of proteins with key cellular functions, which form a widespread cysteine-based cellular network (CYSTEINET). This network may represent an ancestral down-top system composed by a complex matrix of proteins with very different cellular functions, but bearing the same regulatory thiol radical. These proteins include kinases, proteases, antioxidant enzymes, phosphatases, and other structural proteins that use cysteine residues as cellular sensors that can entangle, at very short time scale (nanoseconds), a lot of very different metabolic, respiratory, transport and mechanical functions in the cell.

Why Cysteine?

Since the emergence of life, redox reactions have been necessaries to fuel metabolism and growth in both prokaryotic and eukaryotic living organisms. The eukaryotic cells use energy-converting enzymes evolved from ancestral enzymes that worked in very low oxygen concentration or in anaerobic conditions. These ancestral proteins did not have to deal with the side reactions related with high oxygen concentrations. Then, different redox adaptations have evolved to avoid the deleterious side-reactions of oxygen. The 1-electron reduction of oxygen by reducing components of different cellular electron-transfer pathways can produce reactive oxygen species (ROS), which may have toxic effects on cellular macromolecules but also can regulate the cellular metabolism directly as well as playing a role in the cellular second messenger systems.

The control of the redox microenvironment occurs in virtue of the interaction of reactive oxygen, nitrogen and sulfur species as well as the modifications of cysteine-containing proteins and peptides. Then, cysteine is one of the major regulators of redox homeostasis in biological systems [1-3], including cysteine dependent

enzymatic and non-enzymatic compounds that form an intricate system working to maintain redox homeostasis [4]. The "redox hypothesis" postulates that the disruption of the function and homeostasis of thiol systems is the key central feature of oxidative stress that contributes to aging and age-related disease [4].

Cysteine is a special amino acid because it contains a reactive sulphydryl or thiol group (SH). Free cysteine possesses low reactivity to undergo redox transitions [5] but the thiol group of cysteine is more reactive than the thioether of methionine from which cysteine is synthesized (Fig. **1**). Cysteine participates in a variety of reactions because of its ability to exist in different oxidation states, including thiol, disulfide, sulfenate, sulfinate, sulfonate and the thiyl radical (Fig. **2**). This allows cysteine to have a diversity of roles such as structural, contractile, metal-binding and catalytic activities.

It has been shown that cysteine occurrence in proteins appears to correlate positively with the complexity of the organism, ranging between 2.26% in mammals to 0.5% in some members of the Archeabacteria order. Likewise, the comparison of cysteine residues in ribosomal proteins suggests that evolution takes advantage by increasing the use of this amino acid in proteins. In metal-binding proteins and oxidoreductases studied from the majority of organisms, there are two cysteine residues separated by two amino acids. This finding suggests that cysteine appeared in ancient metal-binding proteins first and it was introduced into other proteins later during the evolution [6].

Cysteine is derived from the essential amino acid methionine and thus, it is not considered as essential amino acid. [7]. Cysteine and methionine amount in the diet must be sufficiently high to meet the needs of protein synthesis and the production of other essential molecules that include glutathione, coenzyme A, taurine and inorganic sulfur (Fig. **1**). On the other hand, cysteine levels must also be below the threshold of cytotoxicity. Elevated tissue cysteine levels may lead to autooxidation to form cystine and ROS, oxidation of protein thiol groups, neurotoxicity mediated by NMDA- type glutamate receptors, membrane cystine/glutamate antiporter activity or excessive production of hydrogen sulfide (H_2S). The toxicity of cysteine has been demonstrated in several experimental models and chronically high levels of cysteine have been associated with human diseases including Parkinson and Alzheimer's diseases [8-12]. Cysteine dioxygenase maintain the levels of cysteine catalyzing the addition of molecular oxygen to the thiol group of cysteine to generate cysteine sulfinic acid. This steep represents an irreversible loss of cysteine, which is shuttled into several pathways (Fig. **1**). The liver has the highest amount of cysteine dioxygenase protein

CHAPTER 3

Non-motor Symptoms in Parkinson's Disease and Drug Therapies

Kazuo Abe*

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Abstract: Parkinson's disease (PD) is typically characterized by its motor symptoms, namely rigidity, resting tremor, bradykinesia and postural instability. However, non-motor symptoms (NMS) such as sleep disturbance, pain, constipation, urinary problems and fatigue are integral to PD and are the leading cause of poor quality of life for both people with PD and their caregivers. Although NMS affect almost every patient, they remain under-recognized and under-treated. An evaluation of the treatment consequences of NMS in over 60% of patients revealed that NMS such as apathy, pain, sexual difficulties, bowel incontinence and sleep disorders may not be revealed to health care professionals because the patients are either embarrassed or unaware that the symptoms are linked to PD. This mini-review provides an overview of NMS in PD along with possible drug therapies.

Keywords: Behavior, depression, digestive disturbance, dopamine agonist, fatigue, levodopa, non-motor symptoms (NMS), Parkinson's disease (PD), quality of life (QOL), sensory disturbance, sleep disturbances, zonisamide.

1. INTRODUCTION

In his historical essay on "shaking palsy", James Parkinson described an "involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards and to pass from a walking to a running pace: the senses and intellects being uninjured" [1]. Since then, Parkinson's disease (PD) has been classified as a "movement disorder" with a clinical diagnosis contingent upon the presence of tremor, akinesia, muscle rigidity and loss of the right reflex. The treatment focus of PD has therefore been to primarily improve these "motor syndromes" [1-3].

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The advent of advanced drug therapies for PD has led to improvements in motor function and activities of daily living (ADL) in the early stages of the disease [4-7]. For motor complications (especially dyskinesia), the reported risk factors include higher dosage and longer duration of levodopa treatment, longer duration and severity of PD and younger age at PD onset [8]. Some researchers consider non-motor syndromes as initial sign and symptom of PD [10-13].

This mini-review provides an overview of the non-motor symptoms and signs of PD as well as possible treatments for the same.

2. NON-MOTOR SYMPTOMS AND SIGNS IN PD

The non-motor fluctuations seen during long-term levodopa usage in PD have been categorized as dysautonomic, cognitive/psychiatric and sensory [9]. Although their causes remain obscure, dopaminergic dysfunction appears to be involved. Neuroimaging data have demonstrated dopaminergic dysfunction in the hypothalamus of the parkinsonian brain. It is important to note that in advanced PD, deep brain stimulation of the subthalamic nucleus seems best at alleviating the non-motor fluctuations affecting sensory, autonomic and cognitive function [9].

The amount of non-motor symptoms and signs in PD constantly increases with the accumulation of information on PD clinical pathogenesis. In order to investigate the non-motor symptoms scale for Parkinson's disease (NMSSPD), we investigated the overall frequency of non-motor symptoms and signs using a questionnaire [11, 12]. We investigated neuropsychological signs (e.g., depression, apathy, anxiety, anhedonia, cognitive dysfunction, attention deficit, hallucination, delusion, dementia, delirium, panic disorder), sleep disorders (restless leg syndrome, abnormal behavioral disorders in REM period, insomnia, excessive day time sleep, sleep apnea), dysautonomia (orthostatic hypotension, dysuria, impotent), digestion disorders (drooling, incontinence, dysphagia, dysosmia, visual disorder), behavioral disorders (hypersexuality, compulsive behavior, pathological shopping, pathological gambling) and others (fatigue, weight loss, weight gain) [11-16].

These foregoing investigations identified non-motor signs and symptoms in PD that have been known to affect motor syndromes and quality of life (QOL) [12].

2.1. Neuropsychological Syndromes

PD patients may develop neuropsychiatric syndromes such as hallucinations [17, 18] or depression [19], which can interfere with treatment, care and ADL.

If hallucinations affect ADL, a full explanation to patients and their caregivers may lighten their burdens. If hallucinations in PD require immediate integrative treatment with psychosocial interventions, antipsychotic medications are prescribed in addition to an adjustment of current anti-PD medications. Nonetheless, an adequate L-dopa dose must be maintained to prevent severe off-states [18].

For individuals with PD, depression is quite common. Research suggests that PD itself causes chemical changes in dopamine, serotonin and norepinephrine in the limbic system that may lead to depression. Dopamine and dopamine agonists are used for the treatment of depression [19-22]. In addition, depression in PD has a close relationship with motor dysfunction. Improvement of motor syndromes is therefore a key factor in the improvement of depression in PD.

Anxiety and apathy syndromes are dependent on depression. These signs and symptoms may be found with depression, but may also be found without depression if a full drug therapy for motor syndromes is administered [23, 24].

James Parkinson had initially claimed that PD patients never developed dementia. However, we now know that PD patients may develop frontal lobe dysfunctions such as forgetfulness [25-27]. PD patients have difficulty planning and carrying out tasks. When facing a task or situation on their own, an individual with PD may feel overwhelmed by having to make choices. They may also have difficulty remembering information, or have trouble finding the right words when speaking. To some degree, cognitive impairment affects most PD patients. The same chemical changes that lead to motor symptoms can also result in slowness in thinking [28]. Cognitive impairment in PD is distinct from dementia, which is a more severe loss of intellectual abilities that interferes with daily living so much that it may not be possible for a person to live independently. The causes of cognitive changes in PD remain unclear, but a possible cause is the decreased level of dopamine. However, the cognitive changes associated with dopamine declines are typically mild and circumscribed. It should be noted that PD patients are deeply stigmatized by their disorder and this impairs their cognitive function and increase the burden for caregivers.

2.2. Sleep Disturbance

PD patients have been reported to claim sleep disturbances, as they may have difficulty turning over in their sleep due to increased muscle tonus, may be disturbed in their sleep by pollakisuria, or may have depression [29]. Although non-ergot dopamine agonists such as ropinirole, pramipexole and rotigotine have been known

CHAPTER 4

Alpha 7 Nicotinic Receptor Agonist Modulatory Interactions with Melatonin: Relevance not only to Cognition, but to Wider Neuropsychiatric and Immune Inflammatory Disorders

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Abstract: Recent clinical trials indicate the importance of the agonists at the alpha 7 nicotinic receptor (a7nAChR) in the modulation of cognitive deficits in both Alzheimer's disease and schizophrenia. Such benefits have been modelled on the effects of the a7nAChR agonists in neurons. However, it is of note that the a7nAChR is also a powerful immune and glia regulator, suggesting that some of a7nAChR agonist benefits may be mediated by the suppression of immune and glia reactivity, which is in line with more recent conceptualizations of these disorders that have emphasized the role of these cells. Notably, melatonin, also efficacious across an array of medical conditions, is a significant regulator of a7nAChR levels and activity, with the a7nAChR mediating many of the beneficial effects of melatonin, including in the regulation of mitochondrial functioning.

This chapter focuses on the wide-ranging benefits that may arise from melatonin interactions with the a7nAChR, especially as to how such interactions may impact on the cellular mechanisms of an array of medical conditions. Such interactions are likely to have relevance across a host of neurodegenerative and psychiatric conditions.

Keywords: Alpha 7 nicotinic, Alzheimer's disease, brain, breast milk, depression, glia, immune, melatonin, multiple sclerosis, Parkinson's disease, schizophrenia, treatment.

INTRODUCTION

Recent data shows the alpha 7 nicotinic acetylcholine receptor (a7nAChR) to have an important role in a number of physiological and pathophysiological processes, with clinical relevance to the regulation of cognition in Alzheimer's disease (AD)

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and schizophrenia [1, 2]. Conceptualizations as to how this is achieved have focussed on the role of the a7nAChR in the regulation of neuronal activity [3]. However, the a7nAChR is also a significant regulator of immune cells, including macrophages [4] and T helper (Th) cells [5], as well as having inhibitory regulatory effects in glial cells, including astrocytes and microglia [6, 7]. Circadian melatonin is a significant positive regulator of a7nAChR levels and activity [8]. Although melatonin is associated with beneficial effects across a host of medical conditions [9-12], it is becoming increasingly clear that some of these melatonin benefits may be mediated by its regulation of the a7nAChR in a number of different cell types, *via* the regulation of mitochondrial functioning [13].

This chapter reviews such melatonin interactions with the a7nAChR in different cellular functions, and how such interactions may be important to the course and etiology of a host of medical conditions, including neurodegenerative and psychiatric disorders. Firstly, the a7nAChR is looked at in more detail.

The Alpha 7 Nicotinic Receptor (a7nAChR)

Although the a7nAChR predominantly forms homomeric, rather than heteromeric pentamers, it is able to form heteromeric pentamers [14]. The majority of central cell types express the a7nAChR, as do immune cells and an array of other cell types, including gut cells, the enteric nervous system and the vagal nerve [15, 16]. In neurons, presynaptic a7nAChR activation leads to calcium and sodium influx, which is generally associated with the positive modulation of neurotransmitter release, whilst it is also expressed post-synaptically suggesting a wider role in synaptic plasticity [17]. In astrocytes, activation of the a7nAChR reduces the levels of inflammatory response, including to Alzheimer's disease associated amyloid-beta [6]; whilst in microglia, a7nAChR activation inhibits the levels of pro-inflammatory cytokines induced by lipopolysaccharide (LPS) [18]. The a7nAChR may also play a role in the regulation of neurogenesis, partly by the modulation of astrocyte fluxes [19], as well as more directly *via* effects on the maturation of immature dendritic cells [20]. As such, the a7nAChR is present in all relevant central cell types and plays a significant role in the regulation of crucial central processes.

The a7nAChR is also present in systemic immune cells, including monocytes/macrophages and T cells [21, 22]. Given that recent data shows an important role for such immune cells in the regulation of central processing, including in the pathophysiological processes underlying Alzheimer's disease, Parkinson's disease, depression and multiple sclerosis [23, 24], the a7nAChR will

also have indirect impacts on key central processes *via* such immune cell regulation. As well as directly modulating such systemic immune cells, the a7nAChR also acts *via* key processes involved in immune activation, including inhibiting the immune-activating consequences arising from increases in gut permeability [24]. Such impacts on gut permeability driven immune activation may be inhibited by a7nAChR stimulation, at least in part, *via* the modulation of vagal nerve activity [15]. Some of the effects of the a7nAChR in decreasing blood-brain barrier (BBB) permeability, seem mediated by its activation in the spleen [25], again highlighting the importance of systemic and immune effects on central processes.

Cognition and a7nAChR

Although associated with many clinically relevant processes, including analgesia [26], recent work on the a7nAChR has highlighted its importance in cognition. Preclinical studies have long shown a7nAChR activation to increase aspects of cognition, including recognition memory and cognitive flexibility [27, 28]. Recent clinical trials in Alzheimer's disease and schizophrenia patients have shown a7nAChR agonists to be cognitive enhancers and/or to inhibit neurodegenerative processes [1, 2]. The a7nAChR is also thought to modulate wider cognitive functioning in people with Down syndrome [29], as well as those on the autistic spectrum [30].

Overall, by virtue of its significant regulation of an array of cells, the a7nAChR is an important regulator of many physiological and pathophysiological processes, with consequences for an array of medical conditions. Some of the a7nAChR effects seem *via* its interaction with melatonin, which will be overviewed next.

MELATONERGIC PATHWAYS

Introduction

Melatonin (N-acetyl-5-methoxytryptamine) is a methoxyindole that is primarily known as the 'darkness hormone' when released by the pineal gland following stimulation by norepinephrine (NE). Consequently, melatonin is widely appreciated for its role in the regulation of the circadian rhythm. However, less well appreciated is the data showing melatonin to be released by many different cell types, including enterochromaffin cells of the gut, where melatonin release can be up to 400-fold higher than its maximal release levels by the pineal gland. A growing body of data suggests that melatonin may be released by all mitochondria-containing cells with consequences for a wide array of

CHAPTER 5

Multi-modal Pharmacological Treatments for Major Depressive Disorder: Testing the Hypothesis

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Abstract: Antidepressant medications have been available for more than fifty years, yet the proportion of patients helped by the various classes of these agents has hardly changed at all. This despite greater insight into the disorder at a biological level based on knowledge derived from contemporary advances in neuroscience. Two fundamental issues may lie at the heart of this apparent paradox. First, depression is a highly heterogeneous disorder and almost certainly is not a single 'disease' entity. The diagnosis is based on the clustering of a discrete set of symptoms, within a defined time frame and as such is best described as a syndrome or disorder. The cause(s) of depression remain unknown and are, in all probability, multi-factorial. The identification of bio-marker defined depression sub-groups may aid both more precise diagnoses and better treatment outcomes. Secondly, the development of pharmacological treatments has been limited by the prevailing aetiological hypothesis of the disorder, the monoamine hypothesis. While it is now well recognised that such a postulate is limited in its explanatory power, both for aetiology and treatment, it has, nevertheless, driven drug development for well over five decades. Clearly, while monoamines surely are important in mediating responses to antidepressant medication, they are almost certainly not the only important driver. Thus the shortcomings in such agents have been well recognised almost since their inception. Principal among these drawbacks has been speed of onset of action with full recovery and remission taking several weeks if not months. Additionally, the relative lack of efficacy of medications in all likelihood reflects the heterogeneity of the disorder and the inability to define predictive factors such as symptom patterns, personality variables or biomarkers, which are responsive to particular pharmacological properties of individual medications. Serious adverse events, side effects, cardiovascular safety and multiple potential drug interactions have also been cited as drawbacks of the existing plethora of antidepressant medications. While few medications have yet emerged into clinical practice based on the insights gleaned from recent basic studies, the notion of targeting multiple, relevant sites in the central nervous system to improve treatment outcomes in major depression has produced some new agents. These so called multi-modal antidepressants simultaneously interact with several different receptors and transporter molecules thought to contribute to antidepressant responses. Expanding the effects on central

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monoamine activity through the development of so-called triple reuptake inhibitors has been one multi-modal approach to the treatment of depression. Amitifiadine is the first triple reuptake exemplar to reach early clinical trials. To date clinical outcomes could be described as mixed. Vilazodone and vortioxetine are multi-modal agents which target reuptake mechanisms as well as other neurotransmitter receptors. This review examines the pharmacological properties of these new agents and critically evaluates their efficacy in clinical trials with a particular emphasis on whether the multi-modal approach obviates some of the perceived shortcomings of existing medications. Achievement of high remission rates in depression is increasingly recognised as the bench mark of an efficacious drug. The extent to which these new agents achieve better remission rates can be regarded as a measure of the extent to which the multi-modal hypothesis is realized and may guide treatment approaches into the future.

Keywords: Depression, monoamines, multimodal medications, remission, response, triple reuptake inhibitors, vilazodone, vortioxetine.

INTRODUCTION

Antidepressant medications have been available from the 1950's. Since the introduction of the tricyclic antidepressants and monoamine oxidase inhibitors there has been an evolution of multiple classes of drug each with putatively different mechanisms of action. While the efficacy of antidepressants has at times been questioned, with some analyses suggesting that the drugs are no more effective than placebo [1, 2], they remain one of the mainstays of management of depressive conditions. Antidepressant response depends on the initial severity of the presenting complaints: moderate to severe forms are more responsive than milder forms. The number of patients who achieve adequate remission of symptoms however remains low. In addition to relatively low remission rates antidepressants have some clinically important shortcomings. Among the impediments to use is the inability to match individual patients to a medication *a priori* with the certainty of improvement of the condition. While some progress has been made with respect to personalised medicine in psychiatry [3], choices of medication for the most part remain a 'trial and error' process. Furthermore, despite the diversity of agents the proportion of patients who recover when treated with members of the various classes has hardly changed at all. For example the STAR*D (Sequenced Treatment Alternatives to Relieve Depression) trial found that more than half of all patients treated were considered 'nonresponsive' to first line administration of a selective serotonin reuptake inhibitor (SSRI) [4]. Efficacy does not appear to be particularly different between the different classes of antidepressants: response rates to the first course of medication are relatively similar. At the clinical coal face choices between drugs are often idiosyncratically based on supposed differences in side effect profiles or presenting patient

symptom patterns, which might be perceived as responding differentially to one drug or another. Such clinical practices persist in the face of intensive research into the aetiology of depression at both a psychosocial and neurobiological level. Clearly, research findings so far have not been particularly helpful for improving clinical outcomes for individual patients.

These ambiguities, in all probability, reflect an uncertainty about the nature of depression itself. Most particularly, clinical trials (and indeed most neurobiological studies) regard major depression (MDD) as a unitary disorder. Diagnostic manuals, such as the DSM-V reinforce the unitary notion of disorder whereas earlier version of the manual distinguished melancholia [5]. With respect to the latter, some would regard DSM defined melancholia as a more severe form of MDD lacking the subtleties of the original meaning of the term [6]. Purists would argue that melancholia is a distinct sub-group of depression with characteristic symptoms typified by movement disorder (either psychomotor retardation or agitation) and a neurobiological basal ganglia dopamine dysfunction [7, 8]. Irrespective of these more nuanced approaches it is clear that depression is a highly heterogeneous disorder and almost certainly is not a single 'disease' entity. The diagnosis is based on the clustering of a discrete set of symptoms, within a defined time frame and as such is best described as a syndrome or disorder. The cause(s) of depression therefore remain unknown and are, in all probability, multi-factorial even within apparently clinically distinct sub-groups of patients. The identification of sub-groups of depression defined by reproducible bio-markers would provide uniformity of objective diagnoses and arguably lead to improved medication treatment outcomes within such groups.

Further, the development of pharmacological treatments has been limited by the prevailing aetiological hypothesis of the disorder, the monoamine hypothesis [9]. Succinctly stated in its earliest iteration, the hypothesis posits that depression arises due to a deficiency of noradrenaline (and / or serotonin) at critical synapses in the central nervous system. It was soon recognised that such a postulate was of limited explanatory power, both for aetiology and for treatment. Modifications of the hypothesis to account for the discrepancy between the delayed onset of clinical effects and the almost immediate effects of medications on neurotransmitter concentrations in brain, invoked adaptation of critical central receptors. Principally this involved down-regulation of α2- and β1-adrenoceptors following chronic drug administration but later developments have envisaged a role for serotonergic receptors (5HT2A and 5HT1A) to account for the action of SSRI agents [10]. Neurotrophic factors, pro-inflammatory cytokines and anti-

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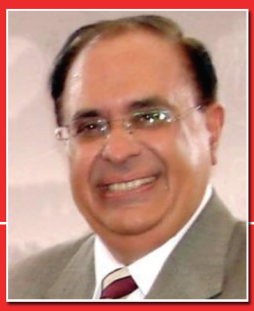

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