A Review of the Potential Role of Nano-Enabled Drug Delivery Technologies in Amyotrophic Lateral Sclerosis: Lessons Learned from Other Neurodegenerative Disorders

ZAMANZIMA MAZIBUKO,[1] YAHYA E. CHOONARA,[1] PRADEEP KUMAR,[1] LISA C. DU TOIT,[1] GIRISH MODI,[2] DINESH NAIDOO,[3] VINESS PILLAY[1]

[1]Wits Advanced Drug Delivery Platform Research Unit, Department of Pharmacy and Pharmacology, Faculty of Health Sciences, School of Therapeutics Sciences, University of the Witwatersrand, Johannesburg, 7 York Road, Parktown 2193, South Africa
[2]Department of Neurology, Division of Neurosciences, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, 7 York Road, Parktown 2193, South Africa
[3]Department of Neurosurgery, Division of Neurosciences, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, 7 York Road, Parktown 2193, South Africa

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ABSTRACT: Amyotrophic lateral sclerosis (ALS) has a multitude of factors implicated in its etiology. The complex neuro-etiology and the restrictive nature of the blood–brain barrier (BBB) have significantly hindered the drug therapy of ALS. Riluzole, a moderately performing drug, is the only agent approved for treating ALS. However, several promising nanocarrier approaches are surfacing that can provide more efficient drug delivery. In addition, biologicals such as stem cells are able to carry neurotrophic factors to their target site, providing motor neurons with the benefits of both, stem cells and neurotrophic factors. This review examines the current drug delivery strategies investigated for optimally treating ALS and related neurodegenerative disorders. Examples include cerium oxide nanoparticles in Alzheimer's disease, odorranalectin, and lactoferrin-coupled PEG–PLGA nanoparticles for urocortin transportation in Parkinson's disease that can also be employed in ALS to bypass the BBB and increase drug bioavailability. A concise incursion into the progress (and lack thereof) made in ALS clinical trials is also discussed. Nanocarriers can potentially eliminate the challenges of poor drug bioavailability in ALS as they have been proven to cross the BBB and reach target sites while minimizing systemic side-effects. Nanocarrier-based delivery of ALS drugs is an area that requires much needed investigation. © 2015 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci
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INTRODUCTION

An unrelenting predicament that has faced physicians and scientist alike is the failure to conquer the on-going complexity of treating central nervous system (CNS) disorders. Most detrimental of these are the neurodegenerative disorders that gradually lead to the loss of bodily functions and eventually death. Neurodegenerative disorders include, but are not limited to, Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS). Extensive research has been carried out in the development of diagnostic tools for early detection as well as successful treatment of these disorders. However, very modest advancement has been achieved. To date, the blood–brain barrier (BBB) remains one of the reasons for the lack of success in the development of treatments as it averts the penetration of therapeutic agents and diagnostic tools. There are a few approaches imminent in tackling the treatment of neurodegenerative disorders including the use of stem cells and antitoxins against mutant forms of the copper and zinc superoxide dismutase (SOD1),[1] as well as nanotechnology which require widespread innovation.

In this review, we look at the various theories for the pathophysiology of ALS and some of the ways these hypotheses led to the various clinical trials. Numerous ALS clinical trials have failed, and for the past decade, only one drug (riluzole) has been approved by the United States Food and Drug Administration (US FDA). The approval of only one drug over the years bears testimony to the very minimal progress that has been achieved in the treatment of ALS. We theorize that some of the unsuccessful therapeutic agents could have prospectively produced better results if firstly clinical trials had suitable, effective designs and secondly, if innovative drug delivery systems were employed to enhance the bioavailability of potential agents. We then look at studies and lessons from similar disorders that incorporate delivery systems to try overcoming the various barriers presented by neurological disorders.

The Hypotheses Surrounding the Cause of ALS

Motor neuron disease (MND) refers to a group of progressive neurodegenerative disorders that are distinguished by the deterioration of upper motor neurons and/or lower motor neurons.[2] Upper motor neurons have cell bodies located in the motor area of the cerebral cortex and have processes connecting with motor nuclei in the brainstem or the anterior horn of the spinal cord, whereas lower motor neurons have cell bodies located in the brainstem or the spinal cord and have axons innervating

Correspondence to: Viness Pillay (Telephone: +27-11-717-2274; Fax: +27-11-642-4355; Email: viness.pillay@wits.ac.za)

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skeletal muscle fibers. However, MND is commonly used to refer specifically to ALS and is the preferred term for this paper. ALS is characterized by the deterioration of both upper and lower motor neurons and presents as spasticity, hyper-reflexia, muscle atrophy, fasciculation, and weakness.[3–5]

The frequency of ALS ranges between 1.5 and 2.5 in 100,000[6] with an average age of onset being between ages 55 and 75 years.[7] The expected survival from the initiation of the symptoms is 3 years.[8] In approximately 90% of the cases, the disease occurs sporadically (sporadic amyotrophic lateral sclerosis) (SALS), whereas the remaining 10% are inherited or familial (familial amyotrophic sclerosis) (FALS).[9] The events underlying the disease triggers are completely unknown in ALS, which makes developing an efficient therapy complicated. Therapies that have been tested for the treatment of ALS range from glutamate antagonists, antioxidants, neurotrophic factors, immunomodulatory agents, and antiviral agents.[4] However, the majority of ALS clinical trials have produced unfavorable outcomes, classifying a large number of agents as non-beneficial. Many of these clinical trials were discontinued because of the severe side-effects caused by these particular therapeutic agents, without any improvement in survival. Various reasons have been suggested for the failure of these clinical trials. The complexity of designing ALS clinical trials and the resulting inconsistent administration of the trials need the most attention. It has been reported that some clinical trials lacked efficient sample sizes, whereas others had contentious duration times as well as ambiguous endpoints,[10] ultimately causing a decrease in statistical significance. Mechanisms that are reported to potentially contribute to the neurodegenerative progression in ALS include cytoskeletal derangements, oxidative stress and mitochondrial dysfunction, protein aggregation, glutamate and excitotoxicity, gene defects, immune dysregulation, and growth factor dysregulation among others. A few of these mechanisms are discussed below.

Oxidative Stress and Mitochondrial Dysfunction

Jones[11] described oxidative stress as "a disruption of redox signalling and control," whereas Sies[12] had previously expressed it to be "an imbalance between the oxidants and antioxidants in favor of the oxidants, potentially leading to damage." Figure 1 summarizes the reactions that generate reactive oxygen species (ROS) and the consequences thereof. The presence of ROS in cells as a result of aerobic metabolism can lead to the escape of some electrons from the mitochondrial respiratory chain, which in turn may result in partial reduction of molecular oxygen during oxidative phosphorylation to finally generate hydrogen peroxide (H_2O_2) and the superoxide radical ion (O_2^-).[13] By definition, the reduction of a portion of oxygen forms superoxide. Characterization of calcium-dependent isoforms of nitric oxide synthase (NOS) has given evidence that suggests that ROS can also be produced by the inflammatory activation of neurons.[14] Peroxynitrite ($ONOO^-$), a potent oxidant, is produced when superoxide reacts with nitric oxide radicals.[15] This highly potent oxidant can cause damage to macromolecules, including DNA, thus possibly leading to DNA mutations.[16] Enzymes in the body, such as SOD, are able to eradicate harmful reactive agents and thus neutralize such reactions.[17]

Several studies have linked oxidative stress in neurons to familial ALS because protein carbonyl groups, which are markers of oxidative stress, were detected in ALS post mortem tissue.[19]

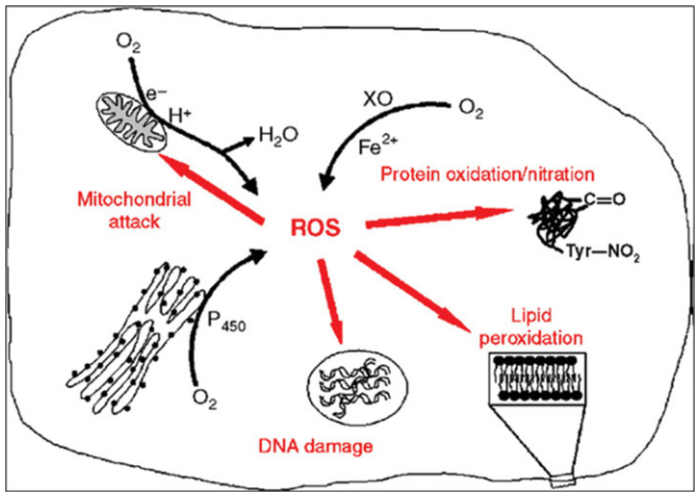

Figure 1. Depiction of the sources of reactive oxygen species (ROS) and their targets. ROS in cells can lead to the escape of electrons from the mitochondrial respiratory chain, which may cause partial reduction of molecular oxygen during oxidative phosphorylation leading to the production of hydrogen peroxide (H_2O_2) and the superoxide radical ion (O_2^-). Oxidative enzymes such as cytochrome P450 in the endoplasmic reticulum, xanthine oxidase (XO), and nitric oxide synthase (not depicted) are responsible for the production of ROS. Cellular targets attacked by ROS include DNA, proteins, membrane lipids, and mitochondria and this attack leads to DNA damage, protein oxidation/nitration, lipid peroxidation, and mitochondrial dysfunction, respectively.[13]

In the brain, the inducible form of NOS has been characterized in microglial cells and its expression described after injury or trauma that results in excess nitric oxide.[14,20] Almer et al.[21] showed the upregulation of inducible nitric oxide in a transgenic mouse model of ALS. Furthermore, increased levels of 8-hydroxy-2′-deoxyguanosine (8-OHdG), an indication of oxidative damage to DNA,[22] have been located in motor cortex of sporadic ALS patients.[23] Additionally, 4-hydroxynonenal (HNE), a neurotoxic marker of lipid peroxidation, was found in increased quantities in lumbar spinal cord as well as CSF of ALS patients.[24,25]

Gene Defects

A number of recognized disease-causing mutations have been recorded in FALS families.[26] These mutations can be inserted into animals to produce an ALS phenotype. Decreasing the assembly of FALS gene products through RNA interference (RNAi) technology or antisense oligonucleotides can delay disease progression in animals.[26] The ALS-causing mutations that occur in the *SOD1* gene are the most widespread and best understood. Over 100 various *SOD1* point mutations can cause an ALS phenotype. These mutations do not appear to result in disease by a loss in function; however, a toxic gain in function for the mutant SOD1 protein is alleged. More recently, the gene encoding a DNA/RNA binding protein FUS/TLS, has been reported to be repeatedly mutated in ALS. This mutation results in the cytoplasmic accumulation of mutant FUS protein, which is characteristic to ALS pathophysiology.[27] It has also been reported that a large hexanucleotide repeat expansion positioned within the non-coding segment of *C9orf72* is the cause of chromosome 9-linked ALS and accounts for 40% of FALS.[28–30]

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