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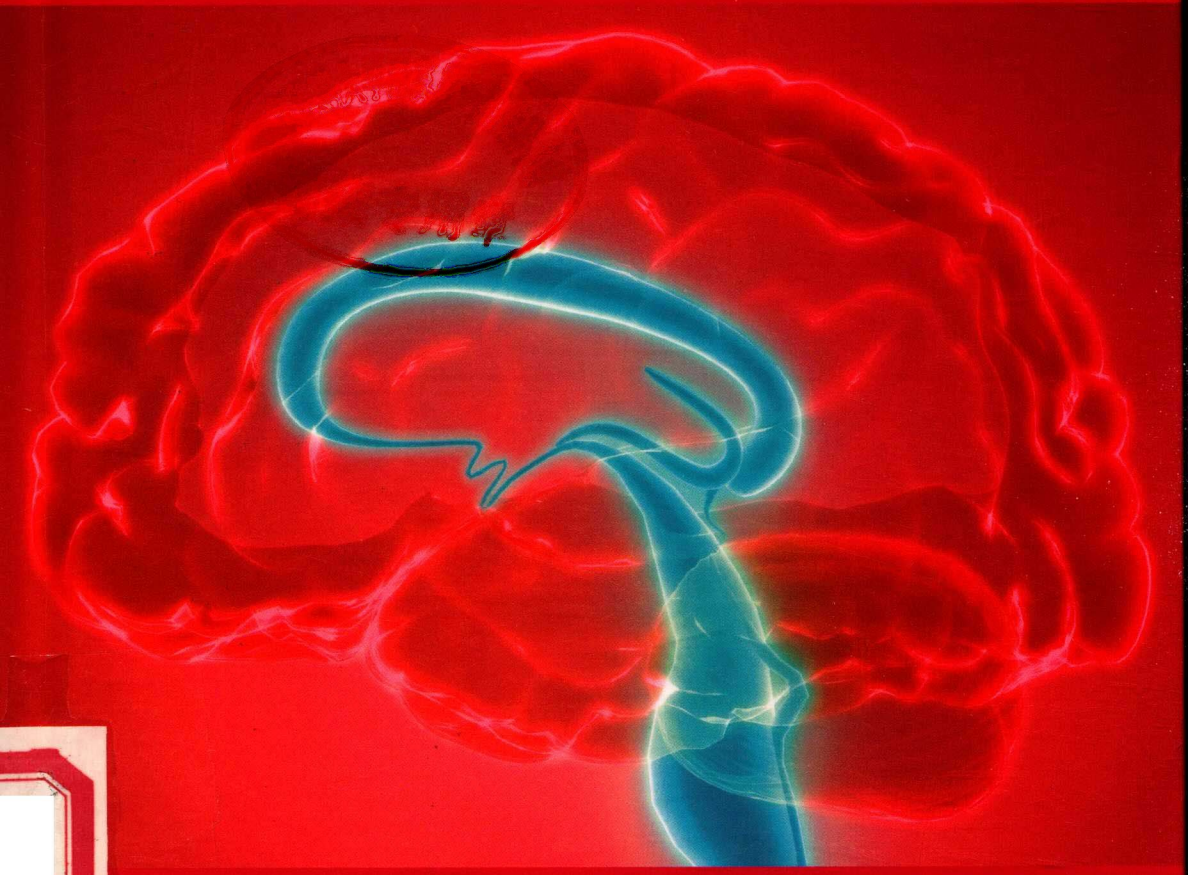

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Nanomedicine in Central Nervous System Injury and Repair

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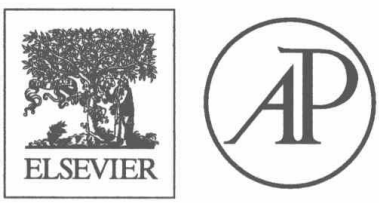

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PREFACE

Recent developments in nanobiotechnology in the field of drug delivery has given new impetus to neuropharmacology for the treatment of diseases afflicting the central nervous system (CNS) for better therapeutic measures (Sharma, 2007, 2009; Sharma, Muresanu, & Sharma, 2017). There are reasons to believe that drugs when administered using nanotechnology are capable to induce superior neuroprotective effects than their parent compounds (Sharma, Muresanu, & Sharma, 2016; Sharma & Sharma, 2012, 2013). This idea is based on the findings that nanodelivered drugs could penetrate faster into the CNS across the blood–brain barrier (BBB) to induce better therapeutic effects. Also nanodelivery of drugs is responsible for a sustained release of the active compound for longer time periods within the CNS for enhanced therapeutic effects (Ruozi et al., 2014; Sharma, Menon, et al., 2016). However, nanodelivery alone could not convert a noneffective drug to the neuroprotective one (Sharma et al., 2009). Thus, selection of specific drugs for nanodelivery is needed to have better therapeutic effects in CSN diseases.

The major problems of preclinical data on neuropharmacology for CNS diseases is largely responsible for a mismatch between bench and bedside experience due to experimental design used for drug development. Thus, almost all drug evaluation across the world for any disease model in academia or industry is based on use of healthy animal models for therapeutic strategy. However, in real human population, several comorbidity factors are often associated with any kind of disease progression and persistence. In most clinical cases of traumatic brain injury (TBI), stroke and other neurodegenerative disease e.g., Alzheimer's disease (AD), Parkinson's disease (PD), and/or Huntington's disease (HD) are often associated with hypertension, diabetes, and other endocrine disorders. In such situations, drug delivery to treat TBI, stroke, AD, or other neurodegenerative diseases alone would not yield desired results in clinical settings. Also, brain pathology associated with any kind of CNS insults results in massive alterations in neurochemical, immunological, electrophysiological, and neurotoxicological elements at the cellular and molecular levels. All these factors markedly alter the homeostasis of the CNS perturbing the extra- and intracellular fluid microenvironment precipitating in disease processes. Accordingly, the brain barrier system comprising the BBB, blood–cerebrospinal fluid (CSF) barrier (BCSFB) as

well as blood–spinal cord barrier (BSCB) is severely compromised (Sharma & Westman, 2003). This will allow entry of several unwanted peripheral factors, i.e., toxins, immunologically active components, neurochemicals, and hormones that will affect cellular functions of the brain leading to disease. Under such situations, any drug affecting only one factor in the brain may not be ideal to treat successfully the devastating acute or chronic neurological diseases. Thus, the time has come to think about use of multimodal drugs that can tackle several key factors for neuroprotection, e.g., neuroregeneration, neuroplasticity, and neuromodulation for better therapeutic strategies. Also, co-administration of drugs is needed to control disease-specific challenges for better therapeutic advances in CNS injury and repair.

Thus, to further enhance patient healthcare in neurological diseases, use of nanomedicine is highly warranted using multimodal drugs in combination with other selective drugs or antibodies for effective therapeutic measures.

This volume deals with use of nanomedicine in CNS injury and repair to expand our current knowledge in the field. The volume is based on six invited and reviewed chapters written by leading experts in the field of nanomedicine in neuroscience. The volume is designed to understand the basic needs of nanomedicine and its usage for the possible therapeutic measures in CNS injury and repair processes in clinical settings based on preclinical data.

Chapter 1 by Gio Tosi (Modena, Italy) deals with current strategies for nanodelivery of enzymes and proteins to the brain for treating brain disorders. Stephen Skaper (Padua, Italy) in Chapter 2 describes new roles of inflammation and the blood–neural barrier (BNB) with reference to novel therapeutic strategies using nanomedicine.

Functionalized magnetic iron oxide nanoparticles (FMIONPs) are commonly used to enhance therapeutic aspects of cancer treatment. Preeti Menon (Uppsala, Sweden) discuss the role of FMIONPs on possible CNS effects in healthy animals and following a focal spinal cord trauma in Chapter 3.

Spinal cord injury (SCI) induces lifetime paralysis depending on the magnitude and severity of the primary insults. Unfortunately, no suitable cure has so far been developed in clinical settings. Thus, exploration of novel drug strategies are still needed in SCI. Hari Sharma (Uppsala, Sweden) in Chapter 4 describes new roles of histaminergic drugs and nanowired delivery in reducing spinal cord pathology in relation to nitric oxide (NO) mediated mechanisms.

Parkinson's disease (PD) affecting the quality of life of several million patients worldwide. However, PD patients still require new therapeutic

tools for therapy. Chapter 5 by José Vicente Lafuente (Bilbao, Spain) discusses nanoformulation for enhanced neuroprotection and neurorestoration in experimental model of PD. The new data clearly suggest superior benefits of using nanodelivery of drugs in PD.

Like PD, AD is a progressive neurodegenerative disease for which no successful treatment regimen has been developed till date. Although, the neurotoxic elements of AD, i.e., amyloid beta peptide (AbP) and phosphorylated tau are well known. In Chapter 6, Aruna Sharma (Uppsala, Sweden) showed that multimodal drug Cerebrolysin that is a balanced composition of several neurotrophic factors and active peptide fragments when administered using TiO_2 nanowired delivery together with histaminergic modulating compounds and/or antibodies to tau protein exerted superior neuroprotective effects in an animal model of AD.

These novel data and ideas presented in the volume will help in better understanding on the use of nanomedicine in CNS diseases in general and neurodegenerative diseases like AD and PD in particular. The volume is an essential collection for study and research in the field of nanomedicine and neurological disease for students, healthcare professionals, lawmakers, teachers, and researchers alike. For neuroscientists from various disciplines such as neuropharmacologists, neuropathologists, neurologists, neurosurgeons, and allied subjects the volume will serve as a ready reference for research and future clinical advances. We hope that this volume will encourage further research in the field for the development of nanomedicine in CNS injury and repair in the near future.

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CONTENTS

CHAPTER ONE

Current Strategies for the Delivery of Therapeutic Proteins and Enzymes to Treat Brain Disorders

Jason T. Duskey[2], Daniela Belletti, Francesca Pederzoli, Maria Angela Vandelli, Flavio Forni, Barbara Ruozi, Giovanni Tosi[1]

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Contents

Abstract

Brain diseases and injuries are growing to be one of the most deadly and costly medical conditions in the world. Unfortunately, current treatments are incapable of ameliorating the symptoms let alone curing the diseases. Many brain diseases have been linked to a loss of function in a protein or enzyme, increasing research for improving their delivery. This is no easy task due to the delicate nature of proteins and enzymes in biological conditions, as well as the many barriers that exist in the body ranging from those in circulation to the more specific barriers to enter the brain. Several main techniques are being used (physical delivery, protein/enzyme conjugates, and nanoparticle delivery) to overcome these barriers and create new therapeutics. This review will cover recently published data and highlights the benefits and deficits of possible new protein or enzyme therapeutics for brain diseases.

[2] Fondazione Umberto Veronesi Fellow.

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