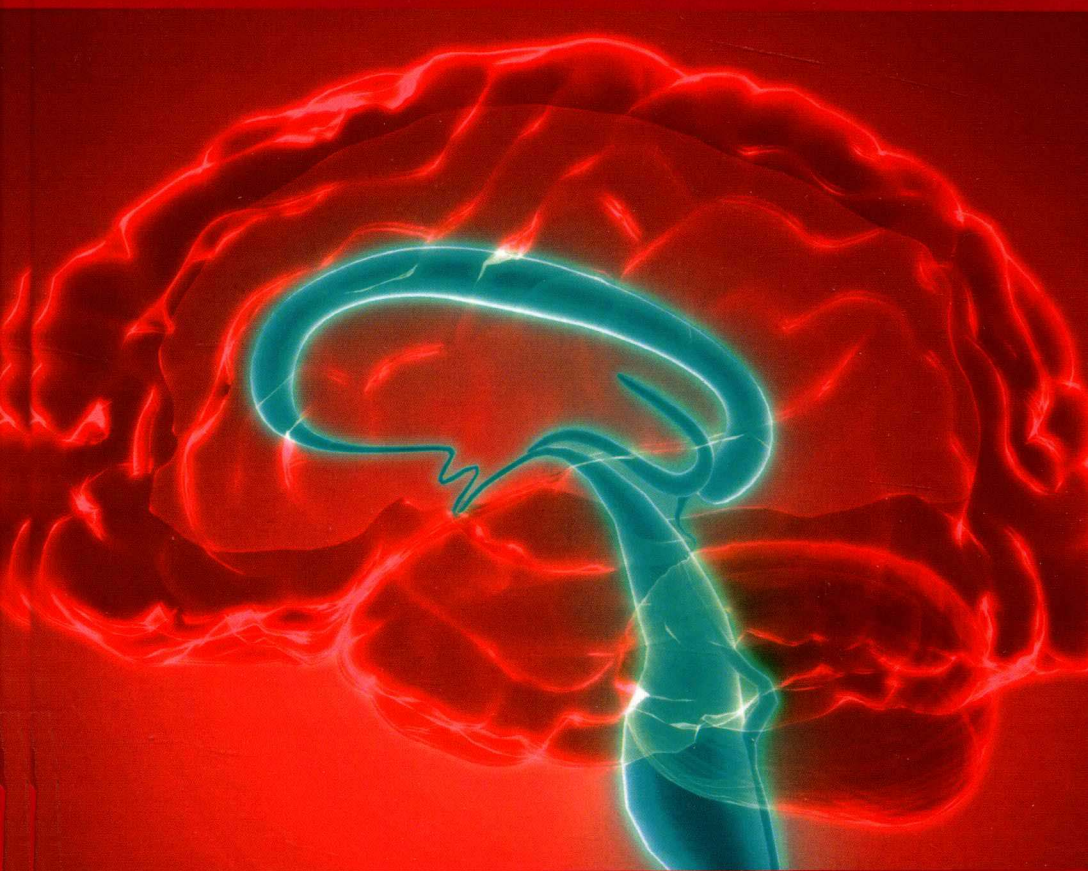


INTERNATIONAL REVIEW OF NEUROBIOLOGY

NANOMEDICINE IN CENTRAL NERVOUS SYSTEM INJURY AND REPAIR
VOLUME 137



EDITED BY
HARI SHANKER SHARMA
ARUNA SHARMA





VOLUME ONE HUNDRED AND THIRTY SEVEN

INTERNATIONAL REVIEW OF NEUROBIOLOGY

Nanomedicine in Central Nervous System Injury and Repair

Edited by

HARI S. SHARMA

*Anesthesiology & Intensive Care Medicine,
Uppsala University Hospital;
International Experimental CNS Injury & Repair (IECNSIR);
Laboratory of Cerebrovascular Research,
University Hospital, Uppsala University,
Uppsala, Sweden*

ARUNA SHARMA

*Anesthesiology & Intensive Care Medicine,
Uppsala University Hospital;
International Experimental CNS Injury & Repair (IECNSIR);
Laboratory of Cerebrovascular Research,
University Hospital, Uppsala University,
Uppsala, Sweden*



ACADEMIC PRESS

An imprint of Elsevier

Academic Press is an imprint of Elsevier
50 Hampshire Street, 5th Floor, Cambridge, MA 02139, United States
525 B Street, Suite 1800, San Diego, CA 92101-4495, United States
The Boulevard, Langford Lane, Kidlington, Oxford OX5 1GB, United Kingdom
125 London Wall, London, EC2Y 5AS, United Kingdom

First edition 2017

Copyright © 2017 Elsevier Inc. All rights reserved.

No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, or any information storage and retrieval system, without permission in writing from the publisher. Details on how to seek permission, further information about the Publisher's permissions policies and our arrangements with organizations such as the Copyright Clearance Center and the Copyright Licensing Agency, can be found at our website: www.elsevier.com/permissions.

This book and the individual contributions contained in it are protected under copyright by the Publisher (other than as may be noted herein).

Notices

Knowledge and best practice in this field are constantly changing. As new research and experience broaden our understanding, changes in research methods, professional practices, or medical treatment may become necessary.

Practitioners and researchers must always rely on their own experience and knowledge in evaluating and using any information, methods, compounds, or experiments described herein. In using such information or methods they should be mindful of their own safety and the safety of others, including parties for whom they have a professional responsibility.

To the fullest extent of the law, neither the Publisher nor the authors, contributors, or editors, assume any liability for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein.

ISBN: 978-0-12-812381-2

ISSN: 0074-7742

For information on all Academic Press publications
visit our website at <https://www.elsevier.com/books-and-journals>



Working together
to grow libraries in
developing countries

www.elsevier.com • www.bookaid.org

Publisher: Zoe Kruze

Acquisition Editor: Sam Mahfoudh

Editorial Project Manager: Andrea Gallego Ortiz

Production Project Manager: Vignesh Tamil

Cover Designer: Greg Harris

Typeset by SPi Global, India



VOLUME ONE HUNDRED AND THIRTY SEVEN

INTERNATIONAL REVIEW OF NEUROBIOLOGY

Nanomedicine in Central Nervous
System Injury and Repair

INTERNATIONAL REVIEW OF NEUROBIOLOGY

VOLUME 137

SERIES EDITOR

PATRICIA JANAK

*Janak Lab, Dunning Hall
Baltimore, MD, USA*

PETER JENNER

*Division of Pharmacology and Therapeutics
GKT School of Biomedical Sciences
King's College, London, UK*

EDITORIAL BOARD

ERIC AAMODT

PHILIPPE ASCHER

DONARD S. DWYER

MARTIN GIURFA

PAUL GREENGARD

NOBU HATTORI

DARCY KELLEY

BEAU LOTTO

MICAELA MORELLI

JUDITH PRATT

EVAN SNYDER

JOHN WADDINGTON

HUDA AKIL

MATTHEW J. DURING

DAVID FINK

BARRY HALLIWELL

JON KAAS

LEAH KRUBITZER

KEVIN MCNAUGHT

JOSÉ A. OBESO

CATHY J. PRICE

SOLOMON H. SNYDER

STEPHEN G. WAXMAN

CONTRIBUTORS

Zoraida P. Aguilar

Ocean NanoTech, Springdale, AR, United States

Maria Angela Vandelli

Te.Far.T.I., University of Modena and Reggio Emilia, Modena, Italy

Daniela Belletti

Te.Far.T.I., University of Modena and Reggio Emilia, Modena, Italy

Harkaitz Bengoetxea

Laboratory of Clinical and Experimental Neuroscience (LaNCE), University of the Basque Country UPV/EHU, Leioa, Vizcaya, Spain

Alejandro Carrasco

Group Nanoneurosurgery, Institute of Health Research Biocruces; Service Neurosurgery, Cruces University Hospital, Barakaldo, Spain

Rudy J. Castellani

Department of Pathology, University of Maryland, Baltimore, MA, United States

Jason T. Duskey

Te.Far.T.I., University of Modena and Reggio Emilia, Modena, Italy

Flavio Forni

Te.Far.T.I., University of Modena and Reggio Emilia, Modena, Italy

José V. Lafuente

Laboratory of Clinical and Experimental Neuroscience (LaNCE), University of the Basque Country UPV/EHU, Leioa, Vizcaya, Spain; Faculty of Health Science, Universidad Autónoma de Chile, Santiago de Chile, Chile

Preeti K. Menon

Anesthesiology & Intensive Care Medicine; Laboratory of Cerebrovascular Research; International Experimental CNS Injury & Repair (IECNSIR), Uppsala University Hospital, Uppsala University, Uppsala, Sweden

Herbert Mössler

“RoNeuro” Institute for Neurological Research and Diagnostic, Cluj-Napoca, Romania; Ever NeuroPharma, Oberburgau, Austria

Dafin F. Muresanu

Department of Clinical Neurosciences, University of Medicine & Pharmacy; “RoNeuro” Institute for Neurological Research and Diagnostic, Cluj-Napoca, Romania

Ala Nozari

Anesthesiology, Massachusetts General Hospital, Harvard University, Boston, MA, United States

Asya Ozkizilcik

Department of Biomedical Engineering, University of Arkansas, Fayetteville, AR, United States

Ranjana Patnaik

School of Biomedical Engineering, Indian Institute of Technology, Banaras Hindu University, Varanasi, Uttar Pradesh, India

Francesca Pederzoli

Te.Far.T.I., University of Modena and Reggio Emilia, Modena, Italy

Catalina Requejo

Laboratory of Clinical and Experimental Neuroscience (LaNCE), University of the Basque Country UPV/EHU, Leioa, Vizcaya, Spain

Barbara Ruozzi

Te.Far.T.I., University of Modena and Reggio Emilia, Modena, Italy

Z. Ryan Tian

Department of Chemistry & Biochemistry, University of Arkansas, Fayetteville, AR, United States

Aruna Sharma

Anesthesiology & Intensive Care Medicine; International Experimental CNS Injury & Repair (IECNSIR); Laboratory of Cerebrovascular Research, Uppsala University Hospital, Uppsala University, Uppsala, Sweden

Hari S. Sharma

Anesthesiology & Intensive Care Medicine; International Experimental CNS Injury & Repair (IECNSIR); Laboratory of Cerebrovascular Research, Uppsala University Hospital, Uppsala University, Uppsala, Sweden

Stephen D. Skaper

University of Padua, Padua, Italy

Giovanni Tosi

Te.Far.T.I., University of Modena and Reggio Emilia, Modena, Italy

Y. Anderw Wang

Ocean NanoTech, Springdale, AR, United States

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 TiO₂ 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.

HARI S. SHARMA

ARUNA SHARMA

Uppsala University, Uppsala, Sweden

REFERENCES

- Ruozi, B., Belletti, D., Forni, F., Sharma, A., Muresanu, D., Mössler, H., et al. (2014). Poly (D,L-lactide-co-glycolide) nanoparticles loaded with cerebrolysin display neuroprotective activity in a rat model of concussive head injury. *CNS & Neurological Disorders Drug Targets*, 13(8), 1475–1482.
- Sharma, H. S. (2007). Nanoneuroscience: Emerging concepts on nanoneurotoxicity and nanoneuroprotection. *Nanomedicine (London, England)*, 2(6), 753–758 [Review].
- Sharma, H. S. (2009). Nanoneuroscience and nanoneuropharmacology. In *Prog Brain Res: vol 180* (pp. 1–264). San Diego, CA: Elsevier Science.
- Sharma, H. S., Ali, S., Tian, Z. R., Patnaik, R., Patnaik, S., Lek, P., et al. (2009). Nano-drug delivery and neuroprotection in spinal cord injury. *Journal of Nanoscience and Nanotechnology*, 9(8), 5014–5037.

- Sharma, A., Menon, P., Muresanu, D. F., Ozkizilcik, A., Tian, Z. R., Lafuente, J. V., et al. (2016). Nanowired drug delivery across the blood–brain barrier in central nervous system injury and repair. *CNS & Neurological Disorders Drug Targets*, 15(9), 1092–1117.
- Sharma, H. S., Muresanu, D. F., & Sharma, A. (2016). Alzheimer's disease: Cerebrolysin and nanotechnology as a therapeutic strategy. *Neurodegenerative Disease Management*, 6(6), 453–456 [Epub 2016 Nov 9].
- Sharma, H. S., Muresanu, D. F., & Sharma, A. (2017). *Drug and gene delivery to the central nervous system for neuroprotection. Nanotechnological advances* (pp. 1–228). Springer Nature, International Publisher.
- Sharma, H. S., & Sharma, A. (2012). Nanowired drug delivery for neuroprotection in central nervous system injuries: Modulation by environmental temperature, intoxication of nanoparticles, and comorbidity factors. *Wiley Interdisciplinary Reviews. Nanomedicine and Nanobiotechnology*, 4(2), 184–203. <https://doi.org/10.1002/wnan.172> [Epub 2011 Dec 8. Review].
- Sharma, H. S., & Sharma, A. (2013). New perspectives of nanoneuroprotection, nanoneuropharmacology and nanoneurotoxicity: Modulatory role of amino acid neurotransmitters, stress, trauma, and co-morbidity factors in nanomedicine. *Amino Acids*, 45(5), 1055–1071. <https://doi.org/10.1007/s00726-013-1584-z> [Review].
- Sharma, H. S., & Westman, J. (2003). *Blood-spinal cord and brain barriers in health and disease* (pp. 1–605). San Diego, CA: Elsevier Academic Press.

ACKNOWLEDGMENTS

We are indebted to Peter Jenner, London, UK for the concept and idea of this volume. Hannah Colford and Kirsten Shankland from Elsevier, UK are acknowledged for helping in the initial stage of this book preparation. Excellent support at every stage of the book production and all help by Andrea Gallego Ortiz, Katie Chan, Sam Mahfoudh (Elsevier, UK) and Vignesh Tamil (Elsevier, India) is highly appreciated. Dafin F. Muresanu (Cluj-Napoca, Romania) for valuable suggestions, Asya Ozkizilcik (Fayetteville, AR, USA) for graphics, and Suraj Sharma (Karlskrona, Sweden) for computer assistance is acknowledged with thanks.

HARI S. SHARMA.

ARUNA SHARMA.

CONTENTS

<i>Contributors</i>	<i>ix</i>
<i>Preface</i>	<i>xi</i>
<i>Acknowledgments</i>	<i>xv</i>
1. Current Strategies for the Delivery of Therapeutic Proteins and Enzymes to Treat Brain Disorders	1
Jason T. Duskey, Daniela Belletti, Francesca Pederzoli, Maria Angela Vandelli, Flavio Forni, Barbara Ruozi, and Giovanni Tosi	
1. Introduction	2
2. Physical Delivery	5
3. Nonphysical Methods	11
4. Conclusion	21
References	22
2. Impact of Inflammation on the Blood–Neural Barrier and Blood–Nerve Interface: From Review to Therapeutic Preview	29
Stephen D. Skaper	
1. Introduction	30
2. Blood–Nerve Interface	30
3. Mast Cells and the BBB	33
4. Immune Cell Interactions Amplify Neuroinflammation	34
5. Neuroinflammation and Aging	35
6. Mast Cells and Glia as Therapeutic Targets	37
7. Conclusion and Perspectives	38
Acknowledgments	39
Conflict of Interest	39
References	39
3. Intravenous Administration of Functionalized Magnetic Iron Oxide Nanoparticles Does Not Induce CNS Injury in the Rat: Influence of Spinal Cord Trauma and Cerebrolysin Treatment	47
Preeti K. Menon, Aruna Sharma, José V. Lafuente, Dafin F. Muresanu, Zoraida P. Aguilar, Y. Anderw Wang, Ranjana Patnaik, Herbert Mössler, and Hari S. Sharma	
1. Introduction	48
2. Experimental Procedures	52

3. SCI Model	53
4. Nanoparticle Administration	53
5. Treatment With Cerebrolysin	53
6. Effects of Cerebrolysin on BBB/BSCB Permeability	55
7. Conclusion and Future Perspectives	60
Acknowledgments	61
References	61
4. Histaminergic Receptors Modulate Spinal Cord Injury-Induced Neuronal Nitric Oxide Synthase Upregulation and Cord Pathology: New Roles of Nanowired Drug Delivery for Neuroprotection	65
Hari S. Sharma, Ranjana Patnaik, Dafin F. Muresanu, José V. Lafuente, Asya Ozkizilcik, Z. Ryan Tian, Ala Nozari, and Aruna Sharma	
1. Introduction	67
2. Histamine in the Spinal Cord	69
3. Histamine and Nitric Oxide Interaction	69
4. Histamine and the Spinal Cord Microcirculation	70
5. Histamine and the BSCB Permeability	70
6. Histamine and Spinal Cord Edema	71
7. Nanowired Drug Delivery Enhances Neuroprotection	71
8. Our Investigations on Histamine-Receptor Modulation and nNOS Expression in SCI	71
9. Histamine Receptors Influence Spinal Cord Pathology and nNOS Expression	82
10. Histamine-Receptor Modulation and BSCB in SCI	86
11. Histamine-Receptor Modulation and SCBF in SCI	86
12. Histamine-Receptor Modulation and Spinal Cord Edema in SCI	87
13. Histamine-Receptor Modulation and Neuronal NOS Expression in SCI	89
14. Histamine-Receptor Modulation and Neuronal Changes in SCI	89
15. TiO ₂ -Nanowired Delivery of Histamine H ₂ Receptor Antagonists Has Superior Neuroprotective Effects in SCI	90
16. Functional Significance of Our Findings	90
Acknowledgments	93
References	94
5. Nanoformulation: A Useful Therapeutic Strategy for Improving Neuroprotection and the Neurorestorative Potential in Experimental Models of Parkinson's Disease	99
Jose V. Lafuente, Catalina Requejo, Alejandro Carrasco, and Harkaitz Bengoetxea	
1. Introduction	100

2. Development	103
3. Conclusions	115
Acknowledgments	116
References	116
6. Novel Treatment Strategies Using TiO₂-Nanowired Delivery of Histaminergic Drugs and Antibodies to Tau With Cerebrolysin for Superior Neuroprotection in the Pathophysiology of Alzheimer's Disease	123
Aruna Sharma, Preeti K. Menon, Ranjana Patnaik, Dafin F. Muresanu, José V. Lafuente, Z. Ryan Tian, Asya Ozkizilcik, Rudy J. Castellani, Herbert Mössler, and Hari S. Sharma	
1. Introduction	125
2. Histaminergic Mechanism	126
3. Histamine Actions in the Brain	127
4. Role of Histamine in AD	128
5. Histamine as a Mediator for Peripheral Immune Cells	129
6. Antihistaminergic Drugs	130
7. Antibodies as Promising Tool for Neurotherapeutic Measures	133
8. Historical Perspectives on the Use of Antibodies as Therapy	133
9. Possible Therapeutic Basis of Antibodies	136
10. Antibodies vs Receptor Antagonist Drugs	136
11. Antibodies Neutralize Effects of Endogenous Antigens	137
12. Nanodelivery of Drugs Induces Superior Neuroprotective Effects Than Their Parent Compound	138
13. Antibodies Therapy in AD	138
14. Our Own Investigations in AD With Histaminergic Drugs and Antibodies for Neuroprotection	139
15. AβP Infusion Model of AD	140
16. Nanowired Delivery of Drugs	140
17. Parameters Measured	140
18. BBB Permeability	141
19. Brain Edema Formation and Volume Swelling	141
20. AβP (1–40) Immunohistochemistry	142
21. Neuronal Damages	143
22. Glial Fibrillary Acidic Protein Immunohistochemistry	143
23. Our Observations in AD Using Histaminergic Drugs and/or Antibodies	144
24. Nanowired Cerebrolysin Potentiates Histamine Antibodies-Induced Neuroprotection in AD	151
25. p-Tau Antibodies Reduces Neurotoxicity in AβP Infusion Model of AD	151

26. Nanowired Cerebrolysin Potentiates p-Tau Antibodies-Induced Neuroprotection in AD	152
27. Functional Significance of Our Findings	154
Acknowledgments	157
References	157



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

Jason T. Duskey², Daniela Belletti, Francesca Pederzoli,
Maria Angela Vandelli, Flavio Forni, Barbara Ruozzi, Giovanni Tosi¹

Te.Far.T.I., University of Modena and Reggio Emilia, Modena, Italy

¹Corresponding author: e-mail address: gtosi@unimore.it

Contents

1. Introduction	2
2. Physical Delivery	5
3. Nonphysical Methods	11
3.1 Systemic Delivery	12
3.2 In Vitro Targeting	13
3.3 In Vivo Proteins, Fusion Proteins, and Modified Enzymes	14
3.4 Nanoparticle-Based Delivery	17
4. Conclusion	21
References	22

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.