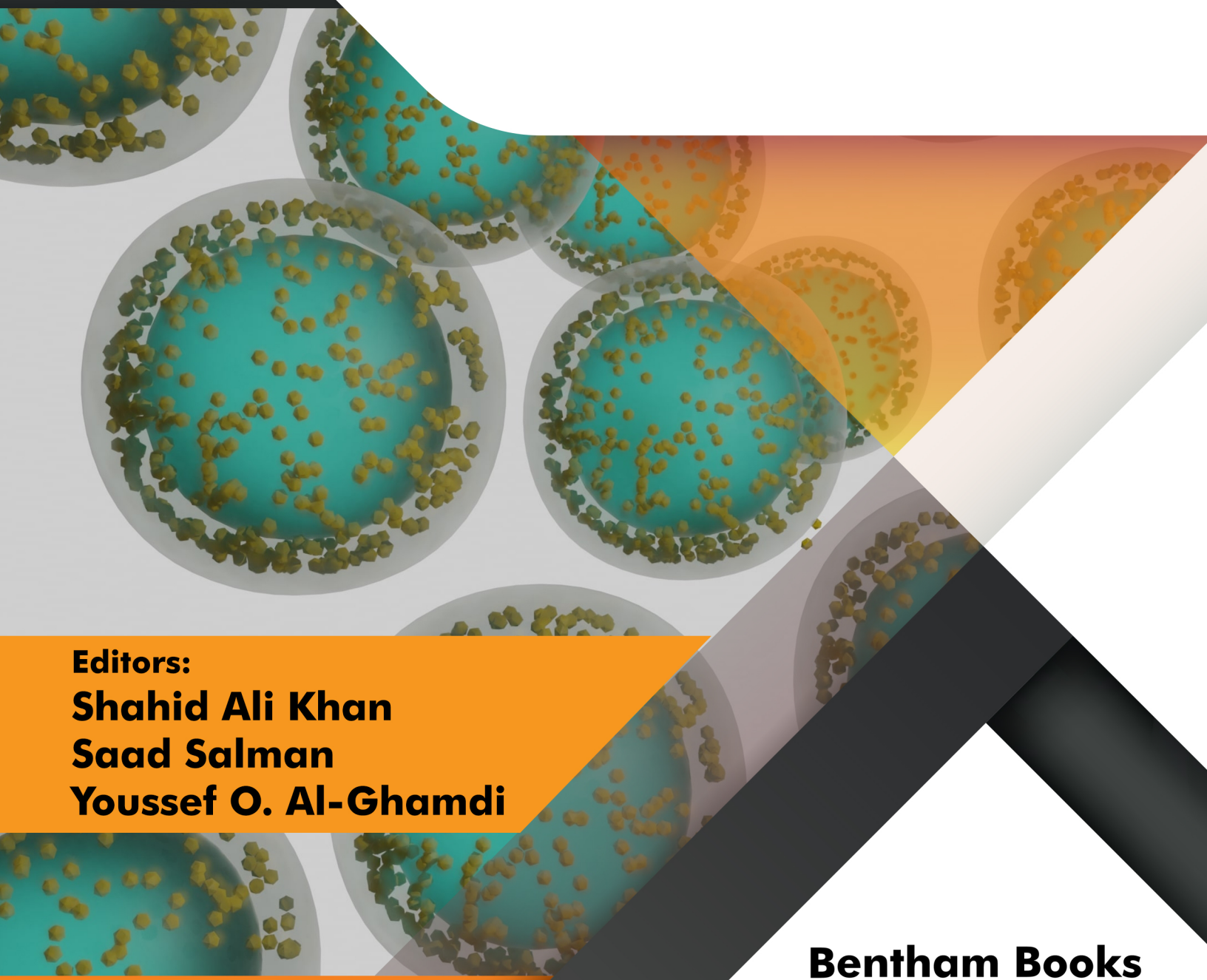
NANOTHERAPEUTIC STRATEGIES AND NEW PHARMACEUTICALS

PART 2



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CONTENTS

PREFACE i

ABOUT THE EDITORS iii

LIST OF CONTRIBUTORS v

CHAPTER 1 NANOTHERAPEUTICS FOR TREATMENT OF NEUROLOGICAL DISORDERS 1

Phoebe Wilson

1. INTRODUCTION 1

2. TRANSPORTATION MECHANISM 2

2.1. Paracellular Transportation 2

2.2. Transcellular Passive Diffusion 3

2.2.1. Transporters 3

2.2.2. Transcytosis 4

3. NPS TYPES 4

3.1. Lipid-Based NPs 5

3.2. Polymeric NPs 6

3.3. Inorganic NPs 7

4. NEUROLOGICAL DISORDERS AND TREATMENT STRATEGIES 8

4.1. Parkinson's Disease 8

4.2. Alzheimer's Disease 8

4.3. Glioblastoma 9

4.4. Vascular Occlusion 9

5. BIOLOGICAL BARRIERS FOR DRUG DELIVERY 10

CONCLUDING REMARKS 11

CONSENT FOR PUBLICATION 12

CONFLICT OF INTEREST 12

ACKNOWLEDGEMENTS 12

REFERENCES 12

CHAPTER 2 MOLECULAR MECHANISM OF THERAPEUTIC ACTIONS OF SOME NANOPARTICLES IN SOME DISEASES 16

Bello Aminu Bello, Ibrahim Khalil Adam, Sani S. Usman, Yahaya Saidu Gwarzo, Luqman Shah and *Fatima Sulaiman Abdullahi*

1. INTRODUCTION 17

2. THE MOLECULAR MECHANISMS OF THERAPEUTIC ACTION OF NPS IN SOME DISEASES 19

2.1. Molecular Mechanism of Anticancer Activities of NPs 19

2.1.1. Molecular Mechanism of Anticancer Activity of AgNPs 20

2.1.2. Molecular Mechanism of Anticancer Activity of AuNPs 24

2.1.3. Molecular Mechanism of Anticancer Activity of Iron Oxide NPs (FeO-NPs) 25

2.1.4. Molecular Mechanism of Anticancer Activity of Titanium Dioxide NPs 26

2.1.5. Molecular Mechanism of Anticancer Activity of Cerium Oxide NPs 27

2.1.6. Molecular Mechanism of Anticancer Activity of Zinc Oxide NPs 27

2.1.7. Molecular Mechanism of Anticancer Activity of Copper Oxide NPs 28

2.2. Molecular Mechanism of Anti-diabetic Activities of NPs 28

2.3. Molecular Mechanism of Anti-bacterial Activities of NPs 30

2.3.1. Molecular Mechanism of Antibacterial Activity of ZnO-NPs 33

2.3.2. Molecular Mechanism of Antibacterial Activity of AgNPs 34

2.3.3. Molecular Mechanism of Antibacterial Activity of AuNPs 36

2.3.4. Molecular Mechanism of the Antibacterial Activity of TiO2-NPs 36
2.3.5. Molecular Mechanism of Antibacterial Activity of NO-NPs 36
2.4. Molecular Mechanism of Anti-fungal Activities of Metallic NPs 37
2.5. Molecular Mechanism of Anti-viral Activities of NPs 37
2.6. Molecular Mechanism of Anti-inflammatory Activities of NPs 38
2.6.1. Anti-inflammatory Activity of ZnO-NPs 42
2.6.2. Anti-inflammatory Activity of AgNPs 45
2.6.3. Anti-Inflammatory Activity of AuNPs 47
2.6.4. Anti-inflammatory Activity TiO_2 NPs 48
2.6.5. Anti-inflammatory Activity of SeNPs 50
CONCLUSION 51
CONSENT FOR PUBLICATION 52
CONFLICT OF INTEREST 52
ACKNOWLEDGMENT 52
REFERENCES 52

CHAPTER 3 NANOTHERAPEUTICS FOR THE TREATMENT OF VOLTAGE GATED ION CHANNELS 72
Fahad Hassan Shah, Song Ja Kim, Muniba Tariq, Sifeng Lucy Chen, Zunaira Afzal, Maham Chaudry, Hassan A. Hemeg, Shahid Ali Khan and *Saad Salman*
1. INTRODUCTION 72
1.1. Background and History of Ion-Channels 72
1.2. Ligand-gated Ion Channels Convert Chemical Signals into Electrical Activities 73
1.3. Biological Role of Ion-Channels 74
1.4. Inhibition of the Sodium-Potassium Pump Causes Delay in the Resting Membrane Potential Decaying Process 75
2. GREEN TECHNOLOGIES FOR STANDARDIZATION 77
3. DEVELOPMENT AND APPLICATION OF POLYMERIC SYSTEM CONTAINING HERBAL EXTRACTS 78
3.1. Microspheres 78
3.2. Hydrogels 79
3.3. Phytosomes (Phyto-Phospholipid Complex) 79
3.4. Emulsions 79
3.4.1. Drug Delivering Systems in Emulsion 80
3.5. Nanoparticles 80
3.5.1. Solid Lipid Nanoparticles 81
3.6. Nanospheres And Nanocapsules 81
3.6.1. Gold and Silver Nanoparticles 81
3.6.2. Injectable Nanoparticles 81
3.6.3. Liposomes 81
3.7. Niosomes 84
3.7.1. Effect of pH on Niosomes 84
CONCLUSION 84
CONSENT FOR PUBLICATION 85
CONFLICT OF INTEREST 85
ACKNOWLEDGEMENTS 85
REFERENCES 85

CHAPTER 4 STIMULI RESPONSIVE HYDROGELS COMPOSITES FOR CONTROL DRUG DELIVERY 92
Zubair Ahmad, Shahid Ali Khan, Youssef O. Al-Ghamdi, Waseeq Ur Rehman, Syed Muhammad Mukarram Shah, Yasir Anwar, Noureen Khan and *Saad Salman*

1. INTRODUCTION 93
2. ROLE OF HYDROGEL IN DRUG DELIVERY 94
2.1. Physically CL Methods for Hydrogel Synthesis 95
2.1.1. CL by Charge Interaction 95
2.1.2. Hydrophobic Interactions 96
2.1.3. Hydrogen Bonding Interaction 96
2.1.4. Stereo Complexation 97
2.1.5. CL via Crystallization 97
2.2. Chemically CL 97
2.2.1. Covalently CL 97
2.2.2. CL by Small Molecules 98
2.2.3. Polymer-polymer CL 98
3. STIMULI SENSITIVE HYDROGELS AND ITS ROLE IN CONTROL DRUG DELIVERY 98
3.1. Light Responsive Hydrogels 99
3.2. pH Sensitive Hydrogels 99
3.3. Thermo Responsive Hydrogels 100
3.4. Electric Signal Stimulated Hydrogels 101
3.5. Glucose Stimulated Hydrogels 102
4. MAGNETIC HYDROGELS NANO CT FOR CONTROL DRUG RELEASE 102
5. CHITOSAN BASED CT HYDROGELS 103
CONCLUSION 104
CONSENT FOR PUBLICATION 105
CONFLICT OF INTEREST 105
ACKNOWLEDGMENT 105
REFERENCES 105

CHAPTER 5 POLYMERIC NANOFIBERS FOR WOUND DRESSING APPLICATIONS 113
Abid Mehmood Yousaf, Yasser Shahzad, Fakhar Ud Din, Qurrat ul Ain Yousafi, Talib Hussain, Muhammad Usman Ghori and *Syed A. A. Rizvi*
1. INTRODUCTION 114
2. ANATOMY OF SKIN 114
3. WOUND 115
3.1. Classification of Wounds 115
3.2. Wound Healing 117
3.2.1. Stages of Wound Healing 118
3.3. Wound Dressing 120
3.3.1. Classification of Wound Dressing 121
3.4. Significance of Wound Dressing 122
4. ANTIMICROBIAL ACTIVITY IMPARTING NFS 123
5. FABRICATION OF NFS 123
6. STRATEGIES TO LOAD ANTIMICROBIAL DRUG ON ELECTROSPUN NFS 124
6.1. Blending 124
6.2. Core-Sheath Fabrication 126
6.3. Encapsulation 126
6.4. Post-treatment 126
6.5. Attachment 127
7. CHARACTERIZATION TECHNIQUES 127
7.1. *In-vitro* Testing 127
7.2. *In-vivo* Testing 128
7.3. Assessment of Antibacterial Activity 132

CONCLUSION 132
CONSENT FOR PUBLICATION 132
CONFLICT OF INTEREST 133
ACKNOWLEDGEMENTS 133
REFERENCES 133

CHAPTER 6 NANO-THERAPEUTICS OF FLAVONOIDS-LOADED POLYMERIC DRUG DELIVERY SYSTEMS 142
Fazle Rabbi, Fahim Ullah Khan, Imad Ahmad and *Amna Nisar*
1. INTRODUCTION 143
2. MEDICINAL PLANTS PHYTOCHEMICALS 145
2.1. Flavonoids and its Properties 146
3. RECENT APPROACHES OF DRUG DELIVERY SYSTEM FOR HERBAL BIOACTIVE SUBSTANCES 147
3.1. Delivery Systems for Enhanced Therapeutic Efficacy and Bioavailability of Flavonoids 148
3.2. NPs Based Delivery of Flavonoids 149
3.3. Polymeric Micelles-based Delivery of Flavonoids 150
3.4. Liposomal Based Delivery of Flavonoids 151
3.5. Self Microemulsifying, Micro-emulsions and Nano-emulsions Based Delivery of Flavonoids 152
3.6. Solid Lipid NPs (SLNS) Based Delivery of Flavonoids 153
3.7. Nanostructured Lipid Carriers (NLCS) Based Delivery of Flavonoids 153
CONCLUSION 154
CONSENT FOR PUBLICATION 155
CONFLICT OF INTEREST 155
ACKNOWLEDGEMENTS 155
REFERENCES 155

CHAPTER 7 ADHD COMORBID TO SUBSTANCE USE DISORDER: A REVIEW OF GENETICS, NEUROBIOLOGY, BRAIN CIRCUITRY, AND NANOTHERAPEUTICS 161
Fahad Hassan Shah, Song Ja Kim, Laiba Wasim, Shanza Nageen, Fakhra Sibtain, Muniba Tariq, Sajid Asghar and *Saad Salman*
1. INTRODUCTION 162
1.1. ADHD, Substance Abuse, and Stimulant Therapy 165
1.2. Risk Factors for ADHD 165
1.2.1. Genetic Susceptibility to Comorbid Attention-Deficit/Hyperactivity Disorder and Heroin Addiction 166
1.2.2. Stress and Mood Reactivity in Addiction 167
1.2.3. Molecular Genetic Studies 169
1.2.4. Clinical Manifestation of ADHD with Heroin Addiction 170
1.3. Behavioral and Brain Functions: An Insight from Animal ADHD Models 173
1.3.1. Animal Models of ADHD 174
2. NANOTHERAPEUTICS FOR ADHD: CHALLENGES, OPPORTUNITIES & PROGRESS 181
2.1. Ginseng 182
2.2. Ginkgo Biloba 182
2.3. Gotu Kola 183
2.4. Guarana 184
2.5. Bacopa Monnier 185
2.6. Rhodiola 186
2.7. Other Herbal Treatments 186
CONCLUSION 191

CONSENT FOR PUBLICATION 196
CONFLICT OF INTEREST 196
ACKNOWLEDGEMENTS 197
REFERENCES 197

CHAPTER 8 SODIUM CHANNELOPATHIES AND NOVEL VIRAL/NON-VIRAL VECTORS FOR THEIR GENE THERAPY 207
Jawaria Idrees, Fahad Hassan Shah, Song Ja Kim, Muniba Tariq, Syed Haroon Khalid, Ikram Ullah Khan, Sajid Asghar and *Saad Salman*
1. INTRODUCTION 208
1.1. Chemogenetics *Vs* Optogenetics 208
2. GENE EDITING 209
3. TYPES OF DIFFERENT VECTOR SYSTEMS FOR GENE DELIVERY 212
3.1. Viral Delivery System 212
3.1.1. Retroviral Vector 212
3.1.2. Adenoviral Vector 212
3.1.3. Adeno-associated Vector 213
3.1.4. Adenoviral Hybrid Vectors 213
3.1.5. Herpes Simplex Vectors 213
3.1.6. POX Virus Vector 214
3.1.7. Lentiviruses Vector 214
3.1.8. Epstein- Barr Virus Vector 214
3.2. Non-Viral Delivery System 215
3.2.1. Physical Methods of Non-Viral Gene Delivery 215
3.3. Chemical Non-Viral Delivery Systems 216
3.3.1. Lipid Polymer Hybrid 217
3.3.2. Cationic Liposomes 217
CONCLUSION 218
FUTURE PERSPECTIVES 218
CONSENT FOR PUBLICATION 219
CONFLICT OF INTEREST 219
ACKNOWLEDGEMENTS 219
REFERENCES 219

CHAPTER 9 GENE THERAPY AND EDITING FOR THE TREATMENT OF SINGLE-GENE PAIN DISORDERS 232
Fahad Hassan Shah, Song Ja Kim, Jawaria Idrees, Muniba Tariq, Syed Haroon Khalid, Ikram Ullah Khan, Sajid Asghar and *Saad Salman*
1. INTRODUCTION 233
2. THE FUNCTION OF ION CHANNELS IN NOCICEPTORS 233
3. TOXINS AND PHARMACEUTICALS AS TARGETS 235
4. TARGETING NAV CHANNELS: LOCAL ANESTHETICS STATE-DEPENDENT ACTION 236
5. MECHANISM OF 6 COUPLINGS (EC) 236
6. ION-SELECTIVITY OF VGSC 236
7. PAIN INSENSITIVITY IN CONGENITAL DISORDERS 238
8. HSAN TYPE IID RESULTING FROM MUTATIONS IN INACTIVATING SCN9A 238
9. THE GAIN OF FUNCTIONAL GENE VARIANT RELATED TO HERITABLE PAIN CONDITIONS 238
9.1. Inherited Erythromelalgia 238
9.2. The Paroxysmal Extreme Pain-disorder 239
9.3. Small-fiber Neuropathy 240

9.4. Familial Episodic Pain and TRAP1 Mutation 241
9.5. Hereditary-Insensitivity to Pain 241
9.6. Innate-pain Insensitivity and SCN9 Amutations Inactivating 242
9.7. SCN11A Mutation and Familial-episodic Pain-syndrome 244
10. BIOPHYSICS OF PAINLESS AND PAINFUL CHANNELOPATHIES 246
11. TREATMENTS FOR THE PAIN CAUSED BY SODIUM CHANNELOPATHIES 248
CONCLUSIONS 249
CONSENT FOR PUBLICATION 249
CONFLICT OF INTEREST 249
ACKNOWLEDGEMENTS 249
REFERENCES 249

SUBJECT INDEX 261

PREFACE

The field of nanotechnology evolved as a discipline and is not a mere specialization. It requires multiple fields such as engineering, physics, chemistry, mathematics, medicine, and pharmacy to be integrated. This book provides a quick review of the practical aspects of these diverse arenas. Advances in nanotechnology have increased the feasibility to tailor the functional modalities that assist in targeting selective biological barriers for drug delivery and other biomedical applications. This book provides knowledge to the students interested in nanotechnology research. This book paves a path between pharmacy and nanoscience while striking an equilibrium between approachability and depth.

All the editors of this book have research collaborations with various local and international universities in the field of nanoscience. They had supervised M. Phil and Ph.D. students in the field of nanoscience and pharmaceutical technology. They had published manuscripts on nanotechnology in Advanced Drug Delivery Reviews and other prestigious journals.

Phoebe's chapter discusses the role of the blood-brain barrier comprising of a highly selective semipermeable border of epithelial cells that shield the brain from substances that impede the transportation of drug delivery used to treat various neurological disorders. Bello et al. reported the molecular mechanisms underlying silver, gold, Iron Oxide, Titanium Dioxide, Cerium Oxide, Zinc Oxide, Nitric oxide-releasing nanoparticles' therapeutic action in cancer, diabetes, bacterial, fungal, viral and inflammatory diseases. The mechanisms of anticancer activity of the nanoparticles ranging from ultra-structure disruption, generation of reactive oxygen species (ROS), induction of DNA damage, inactivation of proteins that regulate signaling pathways, inhibition of migration and angiogenesis as well as induction of apoptosis are debated. Fahad et al. described the delivery of plant-derived nanoparticles comprised of nano-hydrogels, emulsions, and liposomes to targeted sites for disorders of voltage-gated channels. Zubair et al. explained the synthesis techniques pertaining to polymeric injectable hydrogels to reach safely to the targeted site. Abid et al. elucidated the antimicrobial drug-loaded polymeric nanofibers for wound dressing. The technology such as electrospinning and characterization of nanofibers for the drug release, shape, surface quality, ability to endure mechanical shocks, antimicrobial activity, and in vivo wound healing effectiveness are also discussed. Fazle et al. discussed the techniques regarding the synthesis, characterization, and biosafety of flavonoid-loaded polymeric nanoparticles, liposomes, matrix systems, and micro-emulsions by ameliorating their pharmacological activity and reducing the side effects. Jawaria and Fahad et al., in the subsequent two chapters, had described the molecular mechanisms underlying the channelopathies caused by various genetic or acquired factors. Different neurological diseases such as migraine, epilepsy, small fiber neuropathy, paroxysmal pain disorder, dravet syndrome, and congenital insensitivity to pain are explained, and their gene therapy and editing are discussed.

The chapters of this book are written by scientists and researchers of specialized fields and overtly different scientific backgrounds, but everything boiled down to one common goal – Nanoscience. The tremendous consequence of the combined effort led to this book, "Nanotherapeutic strategies and new pharmaceuticals Part 2."

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CHAPTER 1

Nanotherapeutics for Treatment of Neurological Disorders

Phoebe Wilson[1,*]

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Abstract: Our brains are undisputedly regarded as one of the most complex biological structures, therefore it is not surprising that there are challenges associated with the transportation of therapeutic agents across this organ. This may be attributed in large part to the blood-brain barrier (BBB), which maintains a very stable environment in order to sustain normal brain function. The blood-brain barrier is comprised of a highly selective semipermeable border of epithelial cells that shield the brain from unwelcome and invasive substances. It is so effective, however, that it impedes the transportation of drug delivery used to treat various neurological and cerebrovascular disorders, such as Parkinson's Disease (PD), Alzheimer's Disease (AD), stroke, and gliomas (tumors in the brain and spinal cord). Consequently, many central nervous system disorders are undertreated. Significant advances in nanotechnology have increased the feasibility for biomedical applications to the brain, as nanopharmaceuticals may be tailored with functional modalities that assist to target selective brain tissue.

Keywords: Blood-brain barrier, Nanomedicine, Nanotherapeutics, Neurological disorders, Neurovascular, Targeted drug delivery.

1. INTRODUCTION

There is ample evidence to suggest that neurological disorders exist as one of the greatest threats to public health, with recent studies crediting them as the second leading cause of deaths [1]. The increase in patients diagnosed with disorders is contested by the growing demand for effective treatments, which are met with their own obstacles. One of the largest challenges for delivering therapeutic molecules is their inability to breach the blood-brain barrier (BBB). The BBB is formed as astrocytes wrap their "feet" around capillaries in the brain. The tight junctions situated between epithelial cells in the capillary wall, accompanied by the covering comprised of foot-like extensions of the astrocytes, form a barrier

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Shahid Ali Khan, Saad Salman and Youssef O. Al-Ghamdi (Eds.)

that regulates the passage of most ions and molecules between the blood and the brain tissue.

If they were to traverse the brain freely, ions such as sodium (Na^+) and potassium (K^+) could hinder the transmission of nerve impulses. Water, glucose, oxygen, carbon dioxide and small, lipid-soluble molecules are able to diffuse across the barrier with ease. Delivery drugs need to be constructed with optimal lipid solubility in mind, however, this is not a simple feat. By increasing the lipophilicity of the drug through chemical modification, there is a potential risk for decreased systematic solubility, and so the desired pharmacokinetic result may not be obtained.

The introduction of nanotechnology and nanoscience has served as the driving force for developing new strategies to treat neurological conditions. Their ability to penetrate the blood-brain barrier is in large part due to their malleable nature, as they can be modelled into different morphological structures in order to reach their constituent targets. The size of these NPs often resembles biomolecules, which plays a key role in drug targeting. The basis for nanotechnological drug delivery calls for the use of a nanoscopic scale (or nanoscale) and a therapeutic agent, which serve to function as the nanocarrier and the 'consignment', respectively [2]. Both systems' properties are contingent upon whether the drug absorbs into or conjugates to the external surface of the nanoparticle, or instead is enclosed within [2]. These modifications help to supplement blood-brain barrier entry and disease-targeting efficiency [3].

2. TRANSPORTATION MECHANISM

Although the blood-brain barrier provides an impermeable border to particular solutes, brain capillary endothelial cells are able to assist the transcapillary exchange of others. Vital substances such as glucose are able to pass through the barrier in order to facilitate the generation of adenosine triphosphate (ATP) and neurotransmitters. Molecules are able to enter the brain tissue in a paracellular manner, by means of passive diffusion or *via* solute carriers and vesicular transport, as exhibited in Fig. (**1**) [4].

2.1. Paracellular Transportation

Paracellular transport is characterized by the transfer of substances between adjacent epithelial cells [5]. Smaller, hydrophilic materials can passively penetrate the blood-brain barrier through paracellular pathways, while large molecules are restricted due to the tight junctions that are present [6]. For that reason, the

majority of peptides, proteins, and other macromolecules are inhibited from traversing through. Consequently, many problems have arisen from synthesizing these molecules for oral absorption and delivery [5, 6].

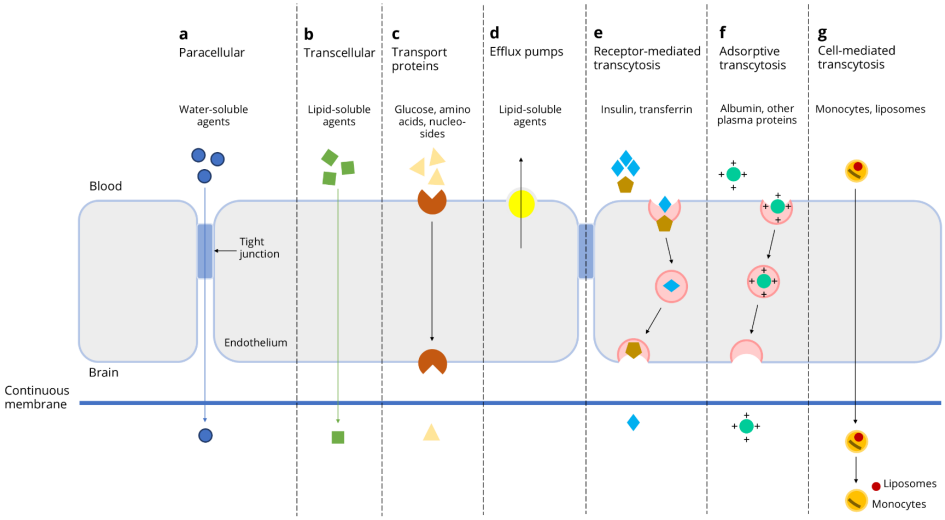

Fig. (1). Transport of substances from blood to brain *via* several routes; paracellular **(a)**, transcellular **(b)**, transport proteins **(c)**, efflux pumps **(d)**, receptor-mediated transcytosis **(e)**, adsorptive transcytosis **(f)** and cell-mediated transcytosis **(g)**.

2.2. Transcellular Passive Diffusion

Transcellular passive enables the interaction between small, hydrophobic molecules and the endothelium of the blood-brain barrier [4, 7]. Drug molecules are able to passively diffuse into the cellular membrane *via* transcellular diffusion. Unfortunately, not all small-scale and hydrophobic molecules are able to diffuse across the endothelial layer, thus prompting further research [8].

2.2.1. Transporters

Transporters are able to assist drug molecules throughout the course of receptor-mediated transcellular crossing [6], as they would otherwise be unable to progress through the blood-brain barrier [4]. In recent years, transporters have aided the bioavailability of nanotherapeutics (NTs) *via* both oral and non-oral distribution

CHAPTER 2

Molecular Mechanism of Therapeutic Actions of Some Nanoparticles in Some Diseases

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Abstract: This chapter covers a detailed description of various molecular mechanisms of therapeutic actions of silver nanoparticles (AgNPs), gold nanoparticles (AuNPs), Iron Oxide nanoparticles (FeO-NPs), Titanium Dioxide nanoparticles (TiO_2-NPs), Cerium Oxide Nanoparticles (CNPs), Zinc Oxide nanoparticles (ZnO-NPs), Nitric oxide releasing nanoparticles (NO-NPs) among others in cancer, diabetes, bacterial, fungal, viral and inflammatory diseases. The mechanisms of anticancer activity of the nanoparticles (NPs) range from ultra-structure disruption, generation of reactive oxygen species (ROS), induction of DNA damage, inactivation of proteins that regulate signalling pathways, inhibition of migration and angiogenesis as well as induction of apoptosis. The mechanism of anti-diabetic activity of the NPs is through inhibition of α-amylase and protein tyrosine phosphatase 1B. The antibacterial and anti-fungal activities of the NPs are by disruption of membrane and induced DNA damage as a result of generation of ROS and dissolved metal ions. The diseases associated with viral infections are treated by restricting the entrance of the virus into the host and by binding to the ap120 site on the viral membrane, thereby regulating its function. The therapeutic mechanism of the NPs in inflammatory diseases is through blocking the production of pro-inflammatory cytokines, inhibiting mast cell proliferation, suppressing lipopolysaccharides (LPS) induced cyclooxygenase (COX-2) gene expression, reducing vascular endothelial growth factor level, decreasing Hypoxia-Inducible Factor (HIF) 1 α -gene expression, suppressing the inducible nitric oxide synthases (INO) gene expression as well as preventing mucin hypersecretion. Therefore, it is clear that the NPs possess various effective and efficient mechanisms of action against both infectious and degenerative diseases.

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Shahid Ali Khan, Saad Salman and Youssef O. Al-Ghamdi (Eds.)

Keywords: Cancer, Diabetes, Diseases, Inflammation, Molecular Mechanism, Nanoparticles, Therapeutic Action.

1. INTRODUCTION

The field nano-biotechnology is considered one of the most dynamic and rapidly growing research fields with diverse applications. It deals with synthesis, strategy and manipulation of new materials at a scale between 1nm and 100 nm [1]. Therefore, the major product of nano-biotechnology called nanoparticles which can be synthesized through different methods that range from physical, chemical, electrochemical, photochemical, biological as well as the use of irradiative techniques [2]. In physical and chemical methods, the involvement of high radiation and high concentrations of both the reductants and stabilizing agents are extremely harmful to the environment, humans and other living organisms, thereby limiting their vast applications [3]. Even though these methods were recorded for being successful in generating pure and well defined NPs, they are highly expensive and release dangerous products to the environment [4]. The biological method, on the other hand, involves a single step bio-reduction process which is cost-effective, can be operated easily at an industrial scale, requires less energy and eco-friendly products (NPs) that are safe for humans with therapeutic importance are generated [5, 6]. Many bio-based substances such as plant extracts, fungi, bacteria, algae and enzymes act as reducing and protecting agents in the green synthesis of NPs [7, 8]. The plant based NPs synthesis is one of the emerging fields of nanotechnology in the recent era [8] that has been continuously drawing the attention of more researchers due to their numerous applications in different fields as a result of their inherent properties and pose no harmful effects to the environment. It is usually carried out at a neutral pH and ambient temperatures [4, 9]. These plant materials or extracts served as both reducing and capping agents for metallic ions have more advantages than other biological material [10]. Because of their safer applications, plant-based metallic NPs are the most demanding and most effective in the field nano-biotechnology. The different metallic NPs are synthesized using metallic ions such as silver, gold, zinc, copper, titanium, magnetite and nickel (Fig. **1**) and different parts of the plants or extracts such as stem, roots, fruits, leaves and flowers are largely investigated with various biological potentials [4].

Due to their completely new and enhanced properties such as their high surface-to-volume ratio and small size, distribution and morphology which allow for the ability to surpass barriers and gain access to biological molecules and, particularly in microorganisms [11], NPs are continuously gaining applications in many fields such as health care, implants, prosthetics, *in-vitro* diagnostics, cosmetics, biomedical, food and feeds, drug-gene delivery, environmental study, mechanics,

optics, optoelectronic devices, bio-imaging devices, sensors and many others [12]. The metallic NPs have been widely used in these fields because of their high stability, solubility, multi-functionality, bio compatibility, adhesive as well as therapeutic properties. The current trend is the development of nanoparticles which have better therapeutic properties as well as being environment-friendly [13 - 15]. Among these metallic NPs, the NPs from noble metals such as gold (Au), silver [1] and platinum (Pt) are well studied and reported to have significant applications in electronics, magnetic, optoelectronics and information storage. Recently, it was reported that, NPs could serve as drug carriers either by active or passive mechanism [1]. The most studied among the metallic NPs are the AgNPs and were reported to be used in producing products that have direct contact with human systems such as shampoos, soaps, detergents, cosmetics, toothpaste, medical, pharmaceuticals, among others [16]. The nanoparticles (NPs) are reported to exhibit a wider range of superior physical, chemical, mechanical, thermal as well as biological properties when compared with the bulk or starting materials. All of these properties are important to the biological and research fields because they influence their antibacterial [17], antifungal [4], anti-inflammatory [18, 19], antiviral [20], anti-diabetic [21], antioxidant [22] and anti-angiogenic potential with improved catalytic activities [15, 23, 24]. AgNPs are reported to have potential applications in cancer diagnosis and treatment [25 - 27]. They are reported to be used in the treatment of ulcer [28 - 30] and cardiovascular disorders [31].

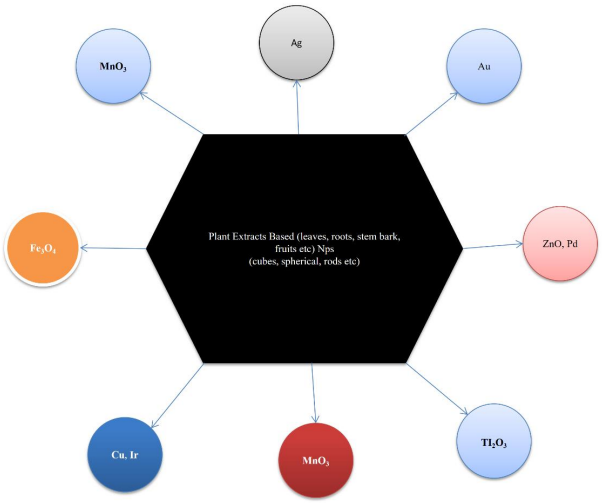

Fig. (1). The metallic-nanoparticles synthesized from different plant extracts.

CHAPTER 3

Nanotherapeutics for the Treatment of Voltage Gated Ion Channels

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Abstract: Nanomedicine is the best way to deliver the plant bioactive to the targeted site. To deliver the plant bioactive in such a small range (10-9) prevents it from many problems like toxicity, less solubility, low permeation through membrane bilayer as well as enhancing the therapeutic activity and bioavailability of the plant drug. Nanotechnologies like liposomes, emulsions, nanoparticles, and hydrogels are proven to transport the plant extracts at the site of action and enhanced their efficacy and efficiency. Nanotechnologies have shown a new picture to achieve the best advantage out of the plant extracts and are serving in the fields of medical, cosmetics, and pharmaceutics.

Keywords: Bioavailability, Nanoparticles, Plant Extracts, Targeted Delivery, Therapeutics.

1. INTRODUCTION

1.1. Background and History of Ion-Channels

In early 1952 , two British biophysicists, Andrew Huxley and Alan Hodgkin

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thoroughly studied the ion channels' current transmission. this study was a part of their Nobel Prize-winning research on the action potential [1]. They used Cole and Baker's research on the voltage-gated membrane pores from 1941, as their basis for further studies [2]. Later in 1970, Ricardo Milediand Bernard Katz used a small signal analysis technique named as the noise analysis to confirm the existence of channels [3]. Another Nobel Prize winning technique was invented by Bert Sakmann and Erwin Neher, the electrical recording technique called "the patch clamp," which showed the existence of the ion channels more clearly and directly [4]. Many researchers continue to push towards understanding the phenomenon upon which these proteins work. With the recent advancement in science and the development of automated patch clamps devices, there is a noticeable increase in the output of the ion channels evaluation. Roderick MacKinnon's reported the physio-chemical properties of ion channel structure and function along with Peter Agre's, who did similar work on aquaporins [5, 6]. Both of them were awarded the Nobel Prize in Chemistry for their commendable work. Furthermore, in 2007, Roderick Mackinnon commissioned Julian Voss-Andreae, to make a sculpture based on the 2001 MacKinnon's group determination of the molecule's atomic coordination.

1.2. Ligand-gated Ion Channels Convert Chemical Signals into Electrical Activities

Synapses are specialized sites for the transmission of neuronal signals between nerve cells. The cells are usually electronically isolated from each other, and the mechanism of signals transmission is usually indirect, and the synaptic cleft segregates the pre- and post-synaptic terminals from each other. The difference in presynaptic-cells electric potential provokes the release of neurotransmitters from the membrane-enclosed granular body *via* exocytosis, in the synaptic cleft. These move towards the post-synapticterminal of the cell by diffusion and generate a difference in its electrical potential. The neurotransmitters, when released, are attacked by specific enzymes in the synapticcleft or they are destroyed by the glial cells, or the neuron terminals take them up. This is done to regulate the neurotransmitter release rate as well as to ensure spatial and temporal signaling at the synapse. Secondly, the chances of the neurotransmitter affecting the surrounding cells are reduced. Thirdly, the synaptic cleft is cleared for the next electrically induced neurotransmitter release. This ensures that the timing of the rapidly repeated signaling event is accurately communicated to the postsynaptic cell. As compared to the direct electrical signalingthrough gap junctions, the signaling by neurotransmitters is far more adaptable and versatile [7].

1.3. Biological Role of Ion-Channels

The transmitter-activated channels mediate conduction across the synapses, underlie the impulse and constitute the most prominent components of the nervous system. By modulation of ion channel conduction-kinetics, many organisms have evolved to produce various types of toxins that shut down the nervous system of the prey [8]. These toxins include the venom of spiders, scorpions, snakes, fish, bees, sea snails, and many other organisms [9]. Similarly, the ion channels play a vital role in the cell cytoskeleton modulation, *i.e*., skeletal, smooth, and cardiac muscle contraction, activation of T-cells, transportation of ions and nutrients across the epithelial layers, and the release of pancreatic beta-cell insulin release, therefore, the ion channels are often targeted in a search for newer drugs [10]. The opening of the ion channels for a short period of time in reply to a stimulus and then returning to its original closed state is the phenomenon of gating. The change in the membrane potential is considered to be the main stimulus that causes the ion channels to open. Continuous stimuli cause the ion channels to deactivate until the stimulus is removed. Ion channels vary between opened and closed configurations and the proteins in the membrane tend to form pores that are hydrophilic in nature. The formation of cytoplasmic extensions by the mechanically gated ion channels form various linkages between the channels and cells' cytoskeleton [11].

The list of the ion channels already depicted has more than 100 entities and this list is ever increasing. The transmission of the electrical impulses in the nervous as well as the muscular system of the body is controlled by these ion channels. Typically, the membrane of even a single nerve cell has about ten different types of channels that are located at different sites on the membrane.The cells that have the ability to be electrically excited are not the only sites where these ion channels are attached rather, they are also present in plants, animals, and even microorganisms [12, 13]. The mimosa plant shows a sudden closure upon being touched, similarly, the paramecium has the ability to reverse its direction upon collision with anything.

Channels possessing the permeability for potassium ions mainly are probably the most common ion channels. In animal cells, even when the membrane is at resting potential, a significant amount of the potassium ion channels are still open and are thus referred to as the potassium-leak channels [14]. These leak channels have the capability of making the membrane much more permeable to the potassium ions as compared to the other ions and this further leads to the membrane potential maintenance of all the plasma membranes in the animal cells.

CHAPTER 4

Stimuli Responsive Hydrogels Composites for Control Drug Delivery

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Abstract: Drug loaded on the injectable polymer hydrogels to reach safely to the targeted site and elute slowly has significant advantages. For this purpose, many techniques have developed for crosslinking (CL) of the polymers chain including physical and chemical CL. Chemical CL (covalent CL) is more effective approach because it provides significant mechanical strength as compared to physically cross-linked hydrogel. There are a number of factors including light, pH, electric current, and glucose are used to stimulate the loaded drug release. For this purpose, various modifications have been made in the hydrogels by changing the CL strategies. In this chapter, a variety of CL techniques have been described along with its advantages and limitations including physically CL, chemically CL, hydrogen-bonding interaction *etc*. Moreover, the response of hydrogels to different stimuli in environment like temperature, pH, electric current, light and glucose sensitivity are also explained with few examples reported in the previous literature. Composite materials (CT) is one of the most emerging materials in various scientific and technological sectors and are effective in various biological applications. Therefore, the CT based hydrogels, are also included in the discussion of this chapter. The role of dexamethasone, methylene blue

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and vitamin B_{12} loading and release *via* CT based hydrogel are described in this chapter.

Keywords: Chitosan, Composites, Cross-linking, Drug Delivery, Hydrogels, Stimuli Responsive.

1. INTRODUCTION

The delivery of pharmaceuticals or drugs at predetermined periods, specific site and with a specific concentration to avail its therapeutic effect in living organisms is known as control drug delivery. It is a slow release of drug in a recommended dosage time [1, 2] which uses carriers for the targeted release of drugs. These carriers convey the drug to the targeted site and release it with predetermined rate.

In a control drug release system, the selected drug slowly eluted due to the response of an external stimuli like temperature, pH and other bimolecular reactions [3, 4]. The releasing action of the drugs is activated during a disease when sensed a signal like increase in temperature during infection, the carrier system evaluate the signal and response to that signal by releasing the drug into required concentration. The carrier system provide a safe environment to the drug against an uncomfortable condition like enzymatic action, temperature increase, buffer action and a variation of pH in stomach *etc* [5, 6]. For this purpose, various carrier system has been adopted to release the drugs at their specific sites.

These carriers include NPs, lipids, bifunctional DNA, self-assembling peptides and polymer hydrogels [7 - 12]. All these carriers have their own advantages and disadvantages. Nowadays polymer-based CTs are widely used for the control drug release. Polymer CTs is a material in which new organic or inorganic fillers introduced with the polymer matrix to increase their mechanical strength, and interfacial interactions of the filler-CT. Various polymer based CTs were reported in the literature including polymer layered silicate [13], chitosan CT and chitosan NPs [14], thermoplastic pastes [15] and hydrogels CTs [3, 16]. The efficiency of these CTs depend on many factors including biocompatibility, elasticity, thermosensitivity and the ability to absorb water to a maximum extent [17].

Hydrogels are three dimensional network of water-soluble polymer characterized by soft and rubbery structure [18]. Hydrogels has the ability to absorbed water efficiently and therefore considered as super absorbent that can be synthesize easily from any water-soluble polymer [17 - 20]. Hydrogels possess diverse biological applications like bio-sensing, wound healing, tissue regeneration, drug delivery *etc* [18, 21 - 26]. Hydrogels in their aqueous environment loaded the specific drug owing to their high porous nature. The porous structure is easily

adjusted by controlling the density and affinity of the CL in gel matrix [27, 28].

During the targeted drug delivery, porosity in the structure of hydrogels played an important role by safe loading of the drug into the gel matrix and then slow release at the targeted site to maintain there a high concentration of the drug [29 - 34].

Chitosan is the natural polysaccharide polymer obtained by the de-acetylation of chitin [35, 36]. It is the second largest polymer by utilization after cellulose. It is insoluble in water, alkali and organic solvents like hexane and benzene [37, 38]. Structurally it consists of hydroxyl and amino groups. The de-acetylation of 2-acetamido-2-deoxy-D-glucose results in chitosan monomer (amido-2-deox--D-glucose). Chitosan offer biodegradability with significant mechanical strength [39 - 41].

It has found that the nano-CTs are more effective as compared to pure material, and that is why the CT based hydrogels releases drug at their appropriate places in the response of external stimuli. Chitosan based nano-CT was found to be an efficient material for the control drug delivery.

In this chapter the hydrogels structure, CL development, response to different, stimuli and their advantages and limitations are discussed. Furthermore, the nano CT based hydrogels for the control drug delivery with specific example are also explained.

2. ROLE OF HYDROGEL IN DRUG DELIVERY

Drug delivery can control by impregnating drug into hydrogels. For this purpose, CL phenomenon are used to produce an elastic characteristic in polymer. Many strategies have been used for developing CL to avail *in situ* gelation. Cross linkers are the molecule having two reactive functional groups responsible for developing a bridge between polymer chains as shown in Scheme. (**1**). The different CL methods available in the literature are discussed below (Scheme. **2**).

CHAPTER 5

Polymeric Nanofibers for Wound Dressing Applications

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Abstract: The broken, ripped or crumbled area of the skin occurr due to laceration, abrasion, incision or excision is called a wound. Speedy and proper wound healing is very important for all types of wounds in order to restore the cosmetic appearance of the skin. Wound healing process is a dynamic and intricate cascade of different steps, including the initiation and termination of numerous cellular mediators. A wound dressing is a germ-free patch or mat placed at the wound site to expedite the healing process and protect the wound from further trauma and infection. A wound dressing patch or mat consisting of antimicrobial drug-loaded polymeric nanofibers (NFs) is an advanced type wound dressing which furnishes several benefits that are usually expected from an ideal wound dressing. Electrospinning methodology is a promising strategy to obtain antimicrobial drug-loaded polymeric nanofibers. Then, these nanofibers are characterized for the drug release, shape and surface quality, ability to endure mechanical shocks, antimicrobial activity, and *in vivo* wound healing effectiveness. Moreover, histopathological explorations might be accomplished in order to assess the actual progress of the healing process in the wound. In particular, the development of a wound dressing using antimicrobial drug-loaded electrospun polymeric NFs is an excellent approach to accomplish speedy healing of wounds and restoration of the skin.

Keywords: Antimicrobial, Electrospinning, Nanofibers, Polymers, Wound, Wound Dressings, Wound Healing.

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Shahid Ali Khan, Saad Salman and Youssef O. Al-Ghamdi (Eds.)

1. INTRODUCTION

2. ANATOMY OF SKIN

The skin is the largest organ of the human body. It wraps the muscles and bones and protects them from the harsh surrounding circumstances. The skin consists of three distinct strata of cells (Fig. **1**). The outer most stratum is epidermis. Below the epidermal layer, exists dermis. Beneath the dermal layer, the hypodermis is located. Different five sublayers of cells, such as corneum, lucidum, granulosum, spinosum and germinativum, can be identified in the epidermal stratum. The types of cells which constitute the epidermal stratum include keratin bearing cells (keratinocytes), melanin or skin colour loaded cells (melanocytes), Birbeck granules carrying dendritic cells (Langerhans cells) and tactile epithelial cells (Merkel-Ranvier cells) [1]. On the basis of the distance from the epidermis, dermal stratum can be either papillary type or reticular type. The hair follicles, glands such as sebaceous glands and sudoriferous glands, and fluid-carrying ducts such as lymphatic vessels and blood vessels are present in the dermal layer of the skin. The connective tissue located in this layer protects the body from external trauma and serves as a shock-absorber [2, 3]. The fibroblast cells, macrophages and adipocytes (fat tissues) are part of the hypodermal layer of the skin. Most of the time, it is considered as a subcutaneous tissue rather than considering it as a segment of the skin. The hypodermal layer is helpful in joining the dermal layer with bones and skeletal muscles. The population of the normal flora and other air-borne common bacteria, such as *Staphylococcus species*, *Bacillus species*, and so on, varies in different areas of the skin [4 - 6]. Gram-positive microbes are usually not harmful when their population is low. On the other hand, gram-negative ones may initiate a serious infection when they invade and enter the circulatory system *via* the broken skin [7].

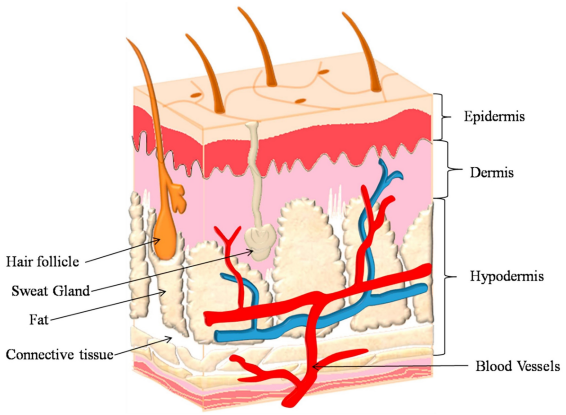

Fig. (1). Anatomy of human skin. Modified with permission from [8].

3. WOUND

The ruptured, tore or crushed area of the skin which results owing to laceration, abrasion or excision of the skin causing injury is known as a wound. Rapid wound healing is very important. An acute wound heals quickly; accordingly, it is likely to be protected from infection by the invading microbes. On the other hand, a chronic wound heals very slowly; therefore, it is more prone to be attacked by infectious bacterial [9]. Wound healing process, usually understood as consisting of a few stages such as hemostasis, inflammation, proliferation and remodeling, is not so simple. It is an intricate process which also encompasses phagocytosis, chemotaxis, and generation of particular stimuli required for initiation and termination of wound healing stages on a certain level of healing [10].

3.1. Classification of Wounds

Wounds can be classified in several ways (Fig. **2**). On the basis of the rapidity of wound healing, a wound might be either an acute wound which heals quickly and without sufficient external support, or it may be a chronic wound that takes a fairly longer period of time to heal [11 - 13]. An acute wound healing process is progressed in proper order of healing stages while chronic wound healing process is not progressed in the order of healing stages [14 - 16]. Moreover, as the acute wounds are healed quickly, they are less prone to be attacked by the bacteria. Conversely, chronic wounds are healed very slowly; therefore, they are more jeopardized by bacterial invasion.

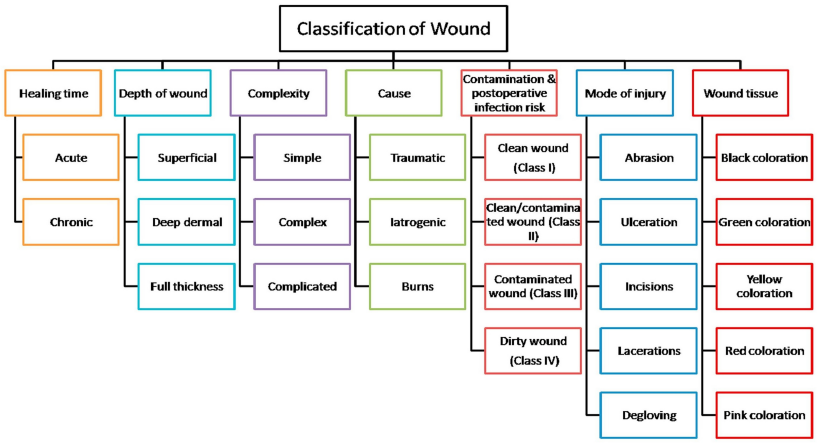

Fig. (2). Classification of wound. Modified with permission from [8].

CHAPTER 6

Nano-therapeutics of Flavonoids-loaded Polymeric Drug Delivery Systems

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Abstract: Plant-based foods contain flavonoids, belonging to the polyphenols class. The phytochemical and phyto-pharmacological sciences advancement has enabled composition elucidation and biological activities of various medicinal plant products. The efficacy of medicinal plants can be measured on the basis of bio-active constituents they comprise. Flavonoid is one of the classes among the bio-active constituents that are hydrophilic in nature. They have low bioavailability and efficacy due to low absorption, as they cannot cross cells lipid membrane due to larger molecular size. A variety of novel drug delivery systems have been developed for polyphenolic compounds to enhance the relative bioavailability. However, if novel drug delivery technology is applied, it may reduce the adverse effects and increase the efficacy of several herbs and their compounds. Herbal medicines were not encouraged for novel formulations development for a long time due to lack of scientific justification and processing difficulties, such as individual drug components identification, extraction and standardization in complex poly-herbal systems. However, advance phytopharmaceutical research can reduce the scientific thirst (*e.g*, pharmacokinetics determination, mechanism of action, the accurate dose required, site of action *etc*.) for herbal medicines to be incorporated in novel drug delivery systems, such as nanoparticles (NPs), liposomes, matrix systems, and micro-emulsions (-E) *etc*. by improving activity by reducing the side effects and required dose. Various drug delivery technologies have been summarized in this chapter which can be used for flavonoids loaded polymeric drug delivery systems.

Keywords: Bioactive Substances, Drug Delivery Systems, Flavonoids, Nanotechnology, Phyto-therapeutics.

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1. INTRODUCTION

The cutting edge in pharmaceutical technology is the development of approaches to produce the "Holy Grail" of medicine under the umbrella of Nanopharmaceutics [1]. Some researchers called it a 'golden touch', in a sense to enhance the value more than the original. Nanotherapeutics is more likely to improve the physicochemical and biopharmaceutical properties of drugs. This approach enhances solubility, pharmacokinetics including half-life, drug release profile, toxicity reduction (acute or chronic), and most strikingly a targeted delivery [2 - 6]. This approach is applicable to both new drug molecules with proven biological activity as well as the existing drugs available in the market [7].

Pharmaceutical industry is making enormous contributions to incorporate these new products on their display. However, there is a limitation in the regulation of nanopharmaceuticals (NPLs), as a limited set of guidelines are available only for compliance with quality and safety, and the clinical trials are mandatory (Fig. **1**). In this scenario, the coming years are expected to get updates on regulation of nanopharmaceuticals and their applied use in clinical settings. Till now NPLs have been used to target cancer, diabetes, respiratory disease, neurodegenerative diseases, infectious diseases, GIT disorders, arthritis, renal disorder and vaccine development [8 - 16].

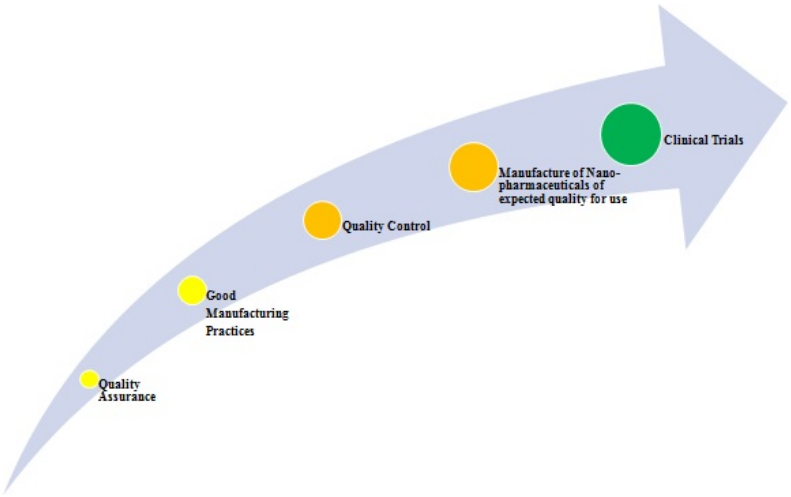

Fig. (1). Nano-pharmaceuticals; on the way to the market.

Natural products have a promising record of achieving a therapeutic goal. To date, almost every pharmacologic class has a history of natural medicine. This is a mature and fully grown area of pharmacology and therapeutics [17, 18]. Phytochemicals had been used actively in their original form, and still now even providing a pharmacophore for designing novel drugs. However, limiting factors give a brake to their use. These factors include solubility, stability, bioavailability, and sometimes, targeted delivery wherever desirable. While moving towards the solution, nanotherapeutics comes first to catch eyesight. Researchers have sort out the problems and are reporting good news from the arena.

The research and development push is focused on the development of new creative and innovative delivery systems for plant-based drugs. Plants-based constituents possess major limitations of instability and low oral bioavailability due to their water solubility nature. These water solvent constituents (*e.g.*, tannins, flavonoids) have poor lipophilicity and large atomic size, which prevents their entrance through the cell membrane [19].

The most appropriate approach to deliver a drug or bioactive (BA) into the body is nanomedicines delivering the drug to achieve concentration (effective) within a therapeutic window over an anticipated period is the proficiency of Nanomedicines (NMs). Essentially, NMs need to be competent enough to deliver a drug to the targeted site. In the previous few ages, NMs had been used by many innovators to deliver plant BA or herbal extracts. Their poor solubility and bioavailability are one of the largest challenges for the usage of herbal BA. These curbs can be fixed by size reduction of BA which improves the solubility and hence bioavailability is increased [1, 2, 4]. Accordingly, it becomes essential to enlarge the boundaries of phytopharmaceuticals prior to therapeutic effectiveness of herbal BA [20].

A carrier of nanometer size is an excellent platform to incorporate a drug or active pharmaceutical ingredient which can then be delivered effectively to the desired site of action. This technology can also be used to deliver natural products that have problems in solubility, stability, toxicity, or any other pharmacokinetic parameter. The efficacy of natural products formulated with NPs solve many such inherent problems, including targeted drug delivery [21].

A well-studied example is ‘Chemoprevention’, an approach in cancer chemotherapy by the use of agents to inhibit, delay, or reverses carcinogenesis before invasion. This Chemoprevention is based on the use of natural phytochemicals that can impede one or more carcinogenetic pathways. The green tea polyphenolic compound epigallocatechin-3-gallate has potent pharmacologic effects. Its use is limited by poor bioavailability. Following the nanotechnology

CHAPTER 7

ADHD Comorbid to Substance Use Disorder: A Review of Genetics, Neurobiology, Brain Circuitry, and Nanotherapeutics

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Abstract: In this chapter, the relationship of neurobiology and brain circuitry of attention deficit hyperactivity disorder (ADHD) and substance use disorder (SUD) along with the heroin addiction (HD) screening similar genetic was examined. The exacerbation of symptoms of SUD and ADHD is also allied with familial and environmental impressions. High-risk factors of ADHD were repeatedly found amid the kinspersons of ADHD descendants. Family and twin studies suggest that genetic and environmental factors have a great influence accounted for about 70-80% of inheritance. Children of SUD and HD parents showed a high rate of ADHD or *vice versa*. Smoking during pregnancy is deliberated to be the prevalent risk for expansion of ADHD. SUD in offspring of parents with the same disorder is validated by many studies that recognized the psychopathology and association of affected parents with their children. The chances of developing ADHD in offspring of those parents who are addicted to heroin are at three times and that of SUD are about sixteen times elevated rates than those having parents with controlled demographic characteristics and proband's comorbidity. The drug purification and withdrawal of SUD often simulate the symptoms of ADHD. The relationship between ADHD and SUD is somewhat complex and multi-faceted. Neuroadaptation in reward and stress pre-dispose an individual to SUD, ADHD, or both are altered. However, a deeper understanding of an alteration in the development of the cortico-cortical and sub-cortical network as ADHD progresses would help in deciding whether dysfunctions of the brain network are the main cause in the pathophysiology of ADHD. Future studies should be more oriented towards the association between cortical, subcortical regions and more resources should be used. The basic action of the herb is to treat the physiological, neurological, and performance parameters. These actions cover the people who are suffering from ADHD and many herbal medicines were used to recognize the stimulant actions. The

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fresh leaves are usually used for performing different activities like anti-spasmodic activity as well as a nutritive nerve tonic. Sedative and stimulating herbs in different combinations are generally used in naturopathic and also in the herbal practice to cure ADHD. The investigation of different stimulants and activities of the herb is used to check the motor functions and performance in the anxiety and anxiety-related disorders' treatment modalities.

Keywords: Attention Deficit Hyperactivity Disorder, Nanotherapeutics, Substance Use Disorder, Treatment.

1. INTRODUCTION

By critical investigation of stimulant pharmacotherapy on children having attention deficit hyperactivity disorder (ADHD) up to adulthood set up no considerable evidence of the infra development of substance use disorder (SUD). To prevent the developing risk of subsequent SUD in children with ADHD it is mandatory treating as soon as possible. Adult Patients with ADHD who already possess SUD are subjected to the effect of treatment; still, some treatment trials assisted did not provide marked results of medication on SUD treatment. In one report cocaine-dependent patients with comorbid ADHD treated with methylphenidate showed a decrease in ADHD symptoms by the remission of cocaine intake. ADHD seems to be frequent uniformly among SUD patients of both genders [1]. Yet on the whole in community samples, males are more usually diagnosed with SUD and ADHD [2, 3]. The aggravation of symptoms of SUD and ADHD are also associated with familial and environmental impact due to maternal and paternal smoking during pregnancy [4]. The probability of ADHD diagnostic criteria meets one in every four SUD patients [5]. It is necessary to artifice appropriate screening assessment procedures and tools to identify patients with comorbid ADHD and SUD. The patient with comorbid SUD and ADHD can effectively be treated by designing a strategic therapeutic plan with cognitive-behavioral therapy (CBT) [6]. An appropriate time for the diagnosis is important for preventing the etiology of the symptoms of ADHD with substance intoxication and withdrawal. An evasion period is supposed to be useful before the diagnosis assessment [7].

The familial basis of ADHD symptoms and genetic clustering and traits aggregation in descendants are completely heritable. High-risk factors of ADHD were frequently found amongst the kinspersons of ADHD progenies. The situation is similar in adolescent and adult twin studies. ADHD is associated with empirical and psychological failures and is eminently heritable in kinspersons [8]. Genetic factors can be greatly influenced by environmental factors. Based on the self-rated analysis, 30-40% heritably was observed in adults whereas manifold

analysis battery, ADHD has the same heritability estimation in adult and child [9]. Pro-band sibling samples and population twin models suggest that ADHD is a composite of one or more distributed traits. Family and twin studies suggest that genetic and environmental factors have a great influence accounted for about 70-80% of inheritance. About 40-60% of heroin addiction is supposed to be a familial inclination, affected by environmental factors, tangled inheritance as well as physiological factors. The addictive familial effects have been associated with genetic-based risk factors like ADHD [10].

Substance use disorder (SUD) is a serious social health problem that merits attention. It is substantially linked with the turbulence of life, neglection, insignificant psychiatric and medical distress emotional chaos, and poor yield [11]. SUD's genetic aggregation has been developed inthe last two decades by comprehensive studies of SUD probands with twain treatment and community setting. A dynamic method of SUD treatment is the early examination of psychiatric manifestations of the progenies due to the influence of maternal psychopathologies. Studies indicated the psychological health issues and social imperfections inherited from SUD-infected parents to their offspring. Studies reported that parents with ADHD are at high risk of developing SUD in their offspring and *vice versa*.

The chances of developing ADHD in offspring of those parents who are addicted to heroin are at three times and that of SUD are about sixteen times elevated rates than those having parents with controlled demographic characteristics and proband's comorbidity. Analogous studies also corroborate similar results that the children of heroin-addicted parents are at higher risk of ADHD than the alcohol-dependent probands [12]. This elevated rate is predicted to be due to environmental plus genetic factors. In another report, the children exposed to stress concerning high-octane events may elicit probands SUD. Conversely, by adjusting the co-parenting situation, offspring will be insignificant to develop ADHD associated with SUD.

Recent research showed that a high-risk factor of SUD was found in ADHD probands. The siblings of ADHD probands were at eloquent risk for SUD, while a second-degree relative was incomparably at lower risk to the risk factor in controls. The literature implied that genetic factors have a detrimental effect on developing comorbid ADHD and SUD than general susceptibility of different psychiatric problems or adverse effects of ADHD pharmacotherapy. Due to these frequent familial consequences, the symptoms elicited from childhood unto adolescence and followed to adulthood. Based on genetic evidence, the comorbidity of SUD and ADHD are extremely inheritable. The prevalence of ADHD is frequent among the probands families of SUD patients while the

CHAPTER 8

Sodium Channelopathies and Novel Viral/non-viral Vectors for their Gene Therapy

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Abstract: Channelopathies are a group of neurological disorders that is caused by various genetic or acquired factors. In this disease, ions channels, a transmembrane protein channel responsible for the regulation of electrochemical gradient in the neuronal cells are disrupted. The disruption leads to myriads of neurological havoc due to abrupt synaptic transmission, voltage potential, and hyperexcitability of ions channels. Defective ions channels expedite the development of various disorders *i.e*., migraine, epilepsy, small fiber neuropathy, erthemalgia, paroxysmal pain disorder, dravet syndrome, and congenital insensitivity to pain, and others. These defects are commonly caused by deleterious mutational events in the ion channel gene encoding regions (SCN9A, SCN10A, and SCN11A). These regions encode for alpha subunits of sodium voltage gated channels (NaV 1.7, 1.8, and 1.9) that have notable importance in normal neuronal functioning. In these regions, usually, missense mutations are observed that cause improper protein folding making sodium channels excited for longer periods. The excitation is mainly manifested in peripheral and sympathetic neurons that contribute towards the development of chronic or acute pain or no pain sensation at all. There are several studies in the pipeline trying to elucidate the molecular mechanism of pain in relation to channelopathies. The lack of efficient pain models and shortcomings in the ill elucidate nature of the disease is somehow impeding the progress and development of novel therapies. But the existing literature revealed various pathways and targets that could be fruitful for different gene therapy interventions as opioids, analgesics, and non-steroidal anti-inflammatory drugs used to treat these conditions are imposing significant side effects and cellular proteins are developing resistance for these molecules, hence making them obsolete.

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Keywords: Channelopathies, Gene Delivery, Ion Channels, Viral and Non-viral Vectors, Voltage Gated Channels.

1. INTRODUCTION

1.1. Chemogenetics Vs Optogenetics

Patients having neuronal channelopathy disorder may seem normal due to homeostatic regulation of membrane potential within acceptable levels. In stress conditions, homeostatic machinery becomes incapable of regulating such abrupt excitability. Factors that are responsible for causing this condition involve erythromelalgia in warm temperatures or periodic paralysis, due to serum potassium fluctuation in channelopathies of food consumptions [1-3]. Optogenetics involves genetic and optical means to regulate neuron excitability by specific resolution of light [4-6]. Different viral vectors are transfected with opsin genes which are acquired from specific microorganisms that target the mammalian brain's specific neurons whose activity can optically inhibit or activated using the light of a specific wavelength [7-9].

The center of attention of *in vivo* optogenetic research is on the expression of channel rhodopsin known as excitatory opsins in inhibitory interneurons or halorhodopsin (inhibitory opsins) in excitatory principal neurons [10-14]. These are one of the techniques used to suppress those areas in the brain which is responsible for causing an epileptic seizure [15-18]. But it is indeterminate to activate which neurons and for how much time period [19]. Some drawbacks of optogenetics areinculcation of rhodopsin in the brain by viral transporters, immunological reaction to these proteins, and other safety concerns associated with viral transporters. The brain perceives light poorly and requires non-mammalian channelrhodopsin to be filled surrounding unwell neurons to stimulate those neurons present in focal areas [20, 21]. Changes governed by optogenetic stimulation in pathological brain networks will either excite or inhibit light-gated ion channels or pumps and thus could be helpful in patients with episodic neuronal channelopathy [22-24]. This enables the normal operation of brain networks all the time, preventing any harmful effect caused by drugs or aberrant regulation of endogenous proteins.

In chemogenetics, a mutation in the ligand binding site of G protein-coupled receptor or ion channels reject the binding of endogenous ligands to these binding-site, therefore, synthetic ligands favorable to mutated receptors are synthesized [25]. Such proteinous ligands are called designer receptors exclusively activated by a designer drug (DREADS) [26].

DREADDs can be designed for the expression of cell-specific type as well as localized cells achieved with virus based vectors [27]. Neurons are transduced which results in chemogenetic protein expression [28]. When exogenous ligand comes in contact with these neurons, they are capable to react in response to membrane potential fluctuations [29, 30]. In the optogenetic method, low wavelength light was delivered to the specific site in the brain for the activation of pumps or channels while DREAD is activated in response to exogenous ligands [25, 31, 32]. DREADS also allows targeted modulation of sensitive areas in the brain [33-35]. Engineered Human Muscarinic receptor hM4Di is one of the examples of DREADD which is resistant to acetylcholine ligand while responding actively to Clozapine and its derivatives [36-38]. CNO mediated activation of HM4Di was proved to treat epilepsy in rodent models. An important advantage of these techniques is that they both efficiently deliver ligands either through light (optogenetics) or exogenous protein (chemogenetics) and are possibly controllable due to closed-loop design coupled with abnormal network excitability [39-41]. Due to improvements being constantly made in closed-loop designs, there will be light weighted, powerful, long-lived battery life and easily implantable gears for efficient transport of drugs as well as light. Some equipment that is implanted in the brain for the detection of seizures, as well as light emissionare restricted to rat models. If the principle of this equipment is completely understood in the coming years, there will be a revolutionary cardiac defibrillator similar implantation device that will allow us to prevent seizures without harming neuronal networks.

2. GENE EDITING

Faulty genes and mutations implicated in neuronal channelopathies can be proficiently edited and corrected using gene-editing tools. The neurological application of these techniques holds certain restrictions that need to be transcended before the translational breakthrough. The protein product of a defective gene can be fixed through several molecular mechanisms. One of them is spliceosome mediated RNA and trans-splicing [42]. Some of the gene-editing tools are Transcription activator-like effector nucleases [43], zinc fingers [44] and the most promising one which is nowadays used is CRISPR-Cas9 technology [45]. Prokaryotes such as Bacteria and Archaea protect themselves from viral and plasmid invasion by activating their innate immune system called CRISPR Cas 9 [46-48]. This revolutionary technology is engineered in such a way that it allows gene editing in mammals. The CRISPR system comprises of two parts: nuclease (Cas9) capable of excising double-stranded DNA while Small guiding RNA guides the Cas9 system for site-specific excision [49].

CHAPTER 9

Gene Therapy and Editing for the Treatment of Single-Gene Pain Disorders

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Abstract: It is a well-known reality that genetic variants can alter the pain perception of an individual in correlation with painless and painful voltage-gated Na-channelopathies for the better understanding of molecular transmission and detection events to noxious stimuli. Mutations in Na_v 1.7 gene coding for the Na-ion channel can cause severe syndromes of distinctive pain such as small-fiber neuropathy, inherited erythromelalgia, and paroxysmal pain disorder. Whereas the inactivation of SCN9A mutations that encodes Na_v 1.7, as a consequence, leads to insensitivity to pain congenitally. The TRPA1 heterozygous mutations code for Nav1.9 (SCN11A) and Nav1.8 (SCN10A) can cause insensitivity to pain while other variants are responsible for the potential-cation channel of the transient-receptor which can cause episodes of familial pain syndromes. Moreover, recently found few other novel genetic polymorphisms essentially identify the severity and complexity of the pain phenotypes. Various pain models for a better understanding of the sensory disorders and heritable disorders of pain are in the developmental phase. Therefore, devising new therapeutic approaches, genome-guided therapy, and understanding the structure of receptors for novel drug development and delivery in correlation with Na-ion channel is imminent.

Keywords: Erythromelalgia, Gene Therapy, Heritable Disorder, Neuropathy, Paroxysmal Pain Disorder, Polymorphisms, Sensory Disorders.

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1. INTRODUCTION

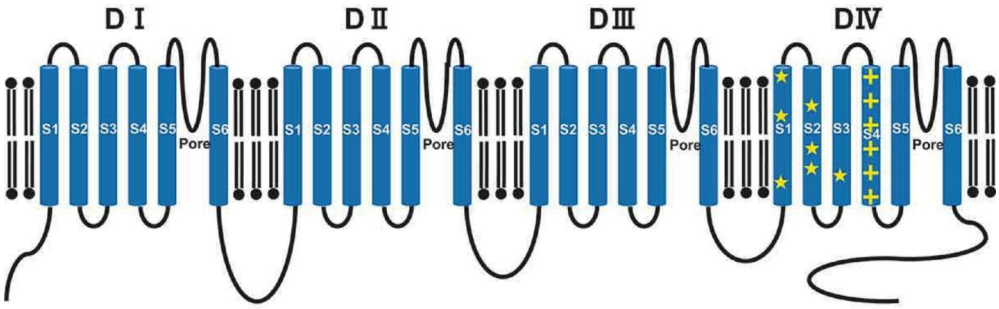
Recent advances are going on in the revelation of subtle hereditary modifications related to the notion of pain in the case of Mendelian disorders [1 - 3]. Modern sequencing, upgraded phenotyping, and bioinformatics tools along with patient pain detection have played a pivotal role in this breakthrough [4]. Genetic mutations can modulate pain insensitivity threshold varying from person to person [5 - 8]. Many hereditary variants are located in genes encoding ion channels; these channels are mostly responsible for the function and excitation of pain receptors. The recessive appearance of these genes 'products in sensory neurons, considered as the basis for analgesic drug discovery programs, play a crucial part in long-term and short-term pain [2, 9 - 11].

The number of chronic pain cases/patients is on the rise all over the world and the treatment is not adequate [12 - 14]. Altered gene expression and function of ion channels cause a common acquired chronic pain state [15, 16]. In this chapter, we will try to understand the basic clinical manifestations and genetics involved in the Mendelian disorders related to conceiving pain along with emphasizing the function of ion channels in all pain states.

2. THE FUNCTION OF ION CHANNELS IN NOCICEPTORS

The term nociceptorwas initially used for sensory neurons that can observe high-intensity stimuli to cause tissue injuries. Mechanical forces, high temperature, a neurotoxin, bio-chemicals including prostaglandins and acids. The stem of nociceptors is located in trigeminal ganglia or dorsal root and the neurons are made of small-diameter myelinated or unmyelinated axons [17 - 20]. The structure of nociceptors is pseudo-unipolar, one axon connects to the peripheral organ, and another axon is connected to the dorsal horn of the spinal cord [21]. The recent findings have made the mechanism of pain detection clear, how it is conveyed to the central nervous system (CNS) that leads to the perception of pain. When nociceptor input signal from any peripheral organ is detected, it undergoes sensitive modulation and processing within the CNS (attentional mechanism, emotional factors, environmental mechanisms, and experience are the determinants of perceived pain [16, 22 - 24]. The role of nociceptors is our point of interest in this case rather than the signaling mechanism. High-intensity signal detection and transmission are significantly regulated by both voltage-gated and ligand-gated ion channels [25 - 28]. Transient receptor potential (TRP) is a prime example of Ion channels. TRPV1 is a non-selective cation channel [29]. It is triggered by low pH, and elevated temperature, the relationship of this channel with nociception was established first [30]. Each TRP channel is synchronized with specific physical or chemical stimuli ranging from high temperature

(TPRV2) and noxious warming (TPRV3), cold, and some other environmental irritants like acrolein (a component of tear gas), cinnamon, mustard, and wasabi triggers TRPV1 activation [31, 32]. Despite being a mechano-transductor, TPRA1 is important for amplifying the response to high-intensity mechanical stimuli. Various subgroups of nociceptors are quite complicated as their expression channels are in a compound or mutual pattern, this difference in morphology is the basis of physiological heterogeneity of Nociceptors (Fig. **1**). For example, polymodal nociceptors are activated by chemical, mechanical, and thermal stimuli, whereas rests do not respond to thermal, and mechanical stimuli exception is in the case of inflammation. Agents involved in transduction are significant as they excite nociceptors through inflammation and injury because of trafficking, interaction with G-protein coupled receptors (GPCR) [33], modified expression, and phosphorylation which conclusively leads to chronic pain situations.



segment	S1			S2			S3
amino acid	D	N	E	N	F	E	D
position in $Na_v1.4$	1356	1366*	1373	1389	1396	1399	1420
position in $Na_v1.5$	1531	1541*	1548	1564	1571	1574	1595*
position in $Na_v1.1$	1544	1554	1561	1577	1584	1587	1608

Fig. (1). Upper panel: Predicted topology of Na_v. Arginine residues of DIVS4 are indicated by + (yellow), and putative gating charge transfer center (pGCTC) of DIVS1-3 are present. Lower panel: Positions of pGCTC of DIVS4 in $Na_v1.4$, $Na_v1.5$ and $Na_v1.1$ are listed. Asterisks indicate the positions at which disease-related mutations were functionally characterized. (Creative Commons CC-BY license) [45 - 50].

Excitation of nociceptors is dependent on sodium channels (Na_v) that are voltage operated [34]. Expression of sodium channel variants 1.7, 1.8, and 1.9 are mostly high in the case of peripheral neurons [6, 35, 36], their properties and patterns of expression are somehow different and they all are related to pain. Axons and peripheral terminal of sensory neurons, nodes of Ranvier are associated with thin myelinated sensory neurons. The central terminal of nociceptors are located in the

SUBJECT INDEX

A

Absorption 3, 148
  oral 3
  poor intestinal 148
Acalypha indica 28
Acetyl-cholinesterase 191
Acid(s) 19, 30, 32, 38, 79, 98, 99, 100, 102, 103, 121, 124, 145, 154, 187, 188, 189, 216, 217, 233
  acrylic 102, 103
  asiatic 189
  carboxylic 99, 100, 188
  fatty 38, 79, 217
  gluconic 102
  hyaluronic 121
  madecassic 189
  methacrylic 100, 102
  nucleic 30, 32, 145, 216, 217
  oleic 154
  phenolic 19, 154
  polylactic-co-glycolic 121, 124
  poly methacrylic (PMA) 100, 102
  selenious 187
  tartaric 98
Acquired chronic pain-syndromes 244
Activation 22, 23, 24, 28, 30, 48, 50, 176, 179, 193, 194, 212, 237, 239, 241, 245, 246
  oncogene 212
  voltage-dependent 237, 239, 241
Activity 23, 24, 25, 27, 29, 30, 32, 35, 82, 83, 162, 182, 185, 189, 191, 192, 247, 248
  acetylcholinesterase 189
  hemolytic 185
  liposomal 82, 83
  of liposomes 82
  of protein tyrosine phosphatase 29, 30
  phagocytic 83
Acute 38, 207
  inflammation 38
  pain 207
Adsorptive-mediated transcytosis (AMT) 3, 4, 6
Agents 27, 31, 37, 38, 39, 47, 189
  antifungal 37
  anti-inflammatory 39, 47
  anti-viral 38
  chemo-therapeutic 31
  memory-enhancing 189
  radio-sensitizing 27
Alzheimer's 1, 8, 9
  disease 1, 8
  treatment 9
Analysis 128, 195
  thermogravimetric 128
  tractography 195
Angiogenesis 16, 20, 23, 24, 46, 51, 119, 130, 149
Anhidrosis 238, 242
Antibacterial 31, 35, 36
  agents 31, 35
  effect 36
Anticancer 16, 19, 20, 21, 24, 25, 26, 27, 28, 37, 83, 150
  activity 16, 19, 20, 21, 24, 25, 26, 27, 28
  agents 83, 150
  hyperthermia therapy 26
Anti-fungal activities 16, 37
Anti-inflammatory 40, 45, 48, 49, 51, 124, 207, 244
  activity 40, 48
  drugs 207, 244
  effects 45, 49, 51, 124
Antimicrobial 51, 113, 121, 123, 128, 129, 132
  polymer-based 132
Antimicrobial 31, 113, 123, 126, 128, 132
  activity 113, 123, 132
  drugs 126, 128
  effect 31
Antioxidant activities 51, 186
Antisense oligonucleotide 83
Antitumor activity 84

Antiviral activity 51
Apoptosis 19, 20, 21, 22, 23, 24, 25, 27, 120, 154
  caspase-dependent 24
  caspase-mediated 25
Application of polymeric system 78
Arterial vascular diseases 10
Arthritis, rheumatoid 39
Asparaginase 28
Aspergillosis 37
Atherosclerosis 39

B

Blood 1, 2, 3, 4, 6, 8, 9, 11, 83, 84, 119
  brain barrier (BBB) 1, 2, 3, 4, 6, 8, 9, 11, 83, 84
  brain tumor barrier (BBTB) 9
  circulatory system 119
Bradycardia 239
Bradykinesia 8
Brain 5, 178, 183, 184, 189
  blood flow 183
  damage 189
  dysfunction 184
  lesions 178
  tumor 5
Byanhidrosis 242

C

Cancer(s) 5, 6, 16, 17, 19, 20, 23, 24, 25, 28, 39, 51, 144, 214
  breast 214
  chemotherapy 144
  prostate 25, 214
  therapy 20, 25, 28
  treatment 6, 19, 20, 23, 24
Cardiovascular disease 9, 19
Carrier-mediated transporter (CMT) 3
Central nervous system (CNS) 1, 11, 183, 184, 187, 188, 213, 214, 233, 245
  disorders 1, 11
Cerebral thrombosis 150
Channelopathies 209, 210, 214, 241
  genetic 210
  neurological 210
  neuronal 209, 214
  painful 241
Charge comparison of cationic liposomes and DNA 217
Cognitive-behavioral therapy (CBT) 162, 166
Coronary heart disease 150
Cytotoxic activity 24

D

Damage 21, 22, 25, 27, 31, 36, 37, 38, 40, 117, 118, 132, 166, 183, 186
  cytogenetic 27
  cytoplasmic organelle 21
  neurological 166
  oxidative 183, 186
  radiation-induced 27
Darvet syndrome 211
Diabetes mellitus (DM) 28
Diagnostic techniques 194
Differential scanning calorimetric (DSC) 127
Diffusion tensor imaging (DTI) 191, 194
Disease(s) 11, 37, 39, 51, 143, 237
  autoimmune 39
  autoinflammatory 39
  celiac 39
  fungal 51
  life-threatening 37
  mechanisms 11, 237
  mutations 237
  neurodegenerative 143
Disorders 1, 11, 18, 39, 43, 143, 149, 161, 164, 165, 166, 168, 170, 171, 173, 181, 183, 185, 189, 208, 232, 238, 241, 242
  cardiac 149
  cardiovascular 18
  cerebrovascular 1
  connective tissue 238
  immune 43
  inflammatory 39
  mental 189

neurobiological 171, 173
neurodegenerative 11, 183
neuronal channelopathy 208
neuropsychiatric 164, 181
oxidative stress-mediated 185
renal 143
sensory 232
Dopaminergic 175, 180, 186
pathways 175
system 180, 186
Dopamine synthesis 178
Doxorubicin hydrochloride drug 96
Dravet syndrome 207
Dynamic light scattering (DLS) 183, 186
Dysfunctions 19, 24, 28, 39, 47, 161, 171, 196, 238, 243
autonomic 243
cardiovascular 39
cognitive 171
endothelial 47
metabolic 28
mitochondrial 24

E

Effector nucleases 209
Effects 29, 77, 79, 84, 85, 93, 176, 179, 182, 183, 184, 188, 189, 191
antidepressant 188
anti-depressant 189
anti-diabetic 29
cognition-promoting 191
noradrenergic 179
therapeutic 77, 79, 84, 93, 176, 182, 183, 184
toxic 85
Electroencephalography 191
Electromagnetic radiations 26
Electromechanical coupling mechanisms 237
Electron-microscopy 235
Electroosmosis 101
Electrospinning 113, 121, 123, 124, 126
methodology 113, 123, 124
polymeric solution 126
process conditions 123
technique 121, 124
Electrospraying 124, 126
Electrostatic force 100, 101
Emotional distress 171
Enzymes 23, 31, 32, 41, 43, 45, 73, 120, 145, 148, 149, 217
caspase-1 43
degradative 217
gastrointestinal 149
hepatic 148
matrix metalloproteinase 120
Erythromelalgia 208, 232, 238, 239, 240
Erythropoietin 216
Exocytosis 4, 73
Expression 23, 209
chemogenetic protein 209
downstream target genes 23

F

Factor(s) 35, 38, 92, 93, 98, 101, 118, 144, 145, 148, 162, 163, 167, 168, 171, 186, 216, 242, 247, 248
chemotactic 118
clotting 118
genetic 162, 163, 167, 168, 171
hemophilia 216
infectious 38
neurotrophic 186, 242
Fatigue, mental 183, 184, 189, 190
Food 6, 34, 104
and drug administration (FDA) 6
industries 104
pathogens 34
Fourier transform 182, 186
analysis 182
infrared spectroscopy 186
Function 31, 37, 38, 47, 171, 172, 174, 175, 176, 177, 181, 183, 187, 189, 195, 196, 233, 240, 244, 245, 249
cognitive 172, 174, 183, 187, 189, 195
cortical 171, 172
inhibitory glutamate 181

pulmonary 47
sensory 240
virus 37
Functional 192, 194
brain imaging 194
communication 194
networking 192

H

Hepatoprotective activity 153
Herbal medicines 142, 145, 148, 161, 187
Hereditary 243, 249
neuropathybothsensory 243
pain disease 249
Heritable disorder 232
Herpes simplex viruses 213
Histoplasmosis 37
Homology-directed repair (HDR) 210
Horseradish peroxidase 98
Human phenotype activity 244
Hydrogen bonding interaction 96, 97
Hydrophobic molecules 3
Hyperhidrosis 243
Hypersensitive 241
Hypertension 124, 150, 177
Hypertriglyceridemia 124
Hypohidrosis 243
Hypoxia-inducible factor (HIF) 16, 20, 46

I

Induce 22, 23, 26, 28, 38
apoptosis 26
cytotoxicity 23, 28
inflammation 38
oxidation 22
Inducible nitric oxide synthases 16, 45, 52
Inflammation 17, 38, 39, 40, 41, 43, 44, 45, 46, 47, 115, 116, 117, 118, 234
protumorigenic 44
Inflammatory 38, 39, 40, 41, 43, 44, 46, 50, 51
bowel diseases 39, 46
cytokines 46
mediator release 38
mediators 44
process 38, 39, 40
responses 39, 40, 43, 50, 51
signals 41
Injectable hydrogels synthesis 96
Insomnia 182
Insulin 30, 118
growth factor 118
receptor kinase (IRK) 30
Interpenetrating polymer network (IPNs) 100, 101
Interstitial 10, 11, 39
cystitis 39
fluid pressure (IFP) 10, 11
Ischemic heart disease 39

K

Kupffer cells 46

L

Langerhans cells 114
Large unilamellar vesicles (LUVs) 5, 6
Liposomal delivery of anticancer medication 6

M

Magnetic resonance imaging (MRI) 7, 9
MAPK 23, 48
pathway 48
signaling pathway 23
Mastocytosis 39
Mechanism 19, 20, 23, 24, 27, 28, 34, 35, 45, 48, 51, 149, 167, 168, 169, 181, 182, 183, 236, 237
anticancer 27, 28
anti-inflammatory 45
anti-proliferative 28
neurobiological 167
of action of AuNPs on cytokines 48

oxidative-defense 183
Medical distress 163
Memory 8, 189, 191
deficits 191
loss 8
retention 189
Mendelian disorders 233
Metabolic syndrome 39
Metabolites, arachidonic acid 44
Microwave-assisted extraction (MAE) 77, 78
Mitogen-activated protein kinase (MAPK) 44, 47, 48
Multi-drug resistance (MDR) 19
Myofibroblasts 120

N

Nanostructured lipid carriers (NLCs) 153, 154
Necrosis 20, 21, 22, 25, 117
Nerve injury 245
Nervous system 74, 181, 218
Neurobiological risk factors 164
Neuroimaging 169, 170
cohorts 169
Neurological diseases 11, 12
Neuropsychological tests 171
Neurotransmitters 2, 8, 73, 164, 167, 175, 176, 183, 185, 186, 189, 218
encapsulating 8
monoaminergic 175
Neurotrophic growth factor (NGF) 238, 242
Neutrophil(s) 41, 44, 50
activity 44
extracellular traps (NETs) 41, 50
Non-steroid anti-inflammatory drugs (NSAID) 39

O

Oil 78, 80, 152, 154, 241
mustard 241

P

Pain 186, 218, 232, 240, 242, 243, 244, 246, 248
distinctive 232
disorder paroxysmal, severe 240
disorders 218, 242, 244
inflammatory 248
natural 186
perceptionof 243
post-mastectomy 246
syndrome 244
transmission 218
Parkinson's disease (PD) 1, 8
Paroxysmal extreme pain-disorder 239
Pathology 11, 211
neurological 11
Pathways 20, 22, 30, 39, 48, 50, 144, 145, 147, 167, 168, 176, 180, 193, 195, 207
carcinogenetic 144
cellular signal transduction 22
flavonoid's biosynthetic 147
mesolimbic dopaminergic 180
metabolic signal-transduction 30
neuronal 167
PEGylated liposomes 78, 82, 83, 84
PEGylation of liposomes 83
Pelvic inflammatory disease 39
Phagocytosis 40, 41, 48, 79, 115, 119
Phosphatidylinositol-dependent kinase 30
Photocatalysis 33
Polymeric 117, 150
micelles-based delivery of flavonoids 150
nanofibers by inflammation 117
Process 19, 23, 27, 40, 41, 43, 78, 97, 115, 119, 124, 125, 127, 210, 216, 217, 246, 248
electrospinning 124, 125, 127
freez-thawing 97
gene editing 210
Production 22, 27, 33, 36, 40, 41, 42, 44, 45, 47, 48, 117, 118
blocking pro-inflammatory cytokines 42
cytokine 44, 47

Pro-inflammatory cytokines 16, 43, 44, 45, 46, 47, 48, 50, 51, 52
activator of 50, 51
production of 16, 43, 45, 47, 48, 52
Properties 27, 34, 98, 143, 149, 151, 182, 188, 189
anti-angiogenic 151
anti-proliferative 149
biopharmaceutical 143
cognitive 189
gel-possessing 98
neuroprotective 182, 188
oxidizing 34
photodynamic 27
Protease-activated receptors (PARs) 50
Proteinases 119
Protein 16, 29, 30, 36, 40, 41, 48 51
corona 40, 41
synthesis 36, 48
tyrosine phosphatase 16, 29, 30, 51
Protein kinase 30, 44, 48
mitogen-activated 44, 48

R

Radiotherapy 19
Reactions 39, 44, 46, 50, 102, 121, 208
allergic 39, 46, 121
anti-inflammatory 40
immunological 208
inflammatory 44, 50
redox polymerization 102
Reactive 16, 20, 22, 25, 27, 31, 34, 35, 37, 41, 47, 50
nitrogen species (RNS) 47
oxygen species (ROS) 16, 20, 22, 25, 27, 31, 34, 35, 37, 41, 47, 50
Receptor-mediated transcytosis (RMT) 3, 4, 6, 8
Release 154, 173 178
glutamate 178
hesperitin 154
psycho-stimulants 178
stimulus-induced 173
Released 50, 126
prothrombin 50
tetracycline 126

S

Scanning electron microscopy 183, 186
Selective 7, 20, 177
inorganic substance 7
serotonin reuptake inhibitors (SSRI) 177
targeting strategy 20
Self nanoemulsifying drug delivery system 80
Sensory modalities 243
Serotonin transport inhibitors (STI) 177
Skin 113, 114, 115, 116, 117, 120, 121, 122, 123, 128, 129, 130, 131, 132, 215, 240
biopsy 240
broken 114
DNA 215
injured 120, 123
Small unilamellar vesicles (SUVs) 5, 6
Spectroscopy 32, 182, 183
electron spin resonance 32
energy-dispersive X-ray 183
mass 182
Staphylococcus aureus 129, 132
Stress 167, 189
and mood reactivity in addiction 167
hormones 189
Supercritical fluid extraction (SFE) 77, 78
Super-paramagnetic iron oxide NPs (SPIONs) 26
Systems 2, 4, 22, 78, 80, 83, 102, 122, 177, 180, 212, 214, 215, 216
adrenergic 177
biodegradable heating 122
body's antioxidant defense 22
developing polymeric 78
mononuclear phagocytic 83

T

Target genes activation 23, 46
Technology 142, 148, 194, 196

neuroimaging 196
novel drug delivery 142, 148
tractography 194
Therapy 9, 26, 162, 182, 184, 187, 213, 232
cellular 9
cognitive-behavioral 162
conventional 182
genome-guided 232
hyperthermia 26
photodynamic 26
Thermo responsive hydrogels 100
Tissue 19, 38, 40, 194
damage 38
debris 40
homeostasis 38
morphology 194
necrosis 19
Tobacco smoking treatment 186
Toll-like receptors (TLRs) 48, 50
Transcytosis 3, 4, 6, 8
adsorptive-mediated 3, 4, 6
receptor-mediated 3, 4, 6, 8
Transmission electron microscopy 21, 32, 183
of cancer cells 21
Transport 10, 79
lipophilic drug 79
transvascular macromolecule 10
Trauma 38, 113, 132
Tumor(s) 1, 8, 9, 10, 11, 19, 23, 24, 26, 84, 150, 151, 216, 212
cell proliferation 23
malignant 19
progression 23
proliferation 24
radiotherapy 8
vaccination 212
Tyrosine phosphatases 47

U

Ulcers 18, 39, 117
diabetic foot 117
peptic 39
Ultrasound-assisted extraction (UAE) 77, 78

V

Vascular endothelial growth factor (VEGF) 16, 23, 46, 52
Voltage-sensing domain (VSDs) 235, 236, 237

W

White 40, 191, 194, 196
blood cells (WBCs) 40
matte, (WM) 191, 194, 196

X

X-ray 76, 127, 128, 184, 235
crystallography 235
diffraction (XRD) 76, 127, 128
diffractometer 184

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