Blood Brain Barrier In Drug Discovery Optimizing Brain Exposure Of Cns Drugs And Minimizing Brain Side Effects For Peripheral Drugs

Drug development for the central nervous system (CNS) has struggled to reach clinical approval. One reason many drugs do not advance into clinical applications is their low uptake in the CNS due to the blood brain barrier (BBB). Targeted drug delivery to the CNS has been well-studied for over 30 years, and recently has been focused on methods of BBB disruption (e.g., focused ultrasound), circumvention (e.g., convection enhanced delivery) or exploitation (e.g., receptor mediated targeting). Receptor mediated targeting is a method of active transport across the BBB by exploiting endogenous receptorligand interactions. The work outlined in this dissertation has studied a novel drug delivery method for receptor mediated targeting through the exploitation of P-glycoprotein (P-gp). P-gp is naturally overexpressed at the BBB and therefore makes an attractive target for CNS drug delivery. It was hypothesized that this new approach to CNS delivery could be accomplished by creating a polymeric nanoparticle delivery system with a P-gp substrate as a targeting moiety. The work focused on the development of a polylactide (PLA) nanoparticle containing a surfacetethered polyethylene glycol (PEG) linker terminated with rhodamine as a P-gp targeting moiety. Rhodamine dyes are a well-known class of P-gp substrates and the two used in this study, rhodamine 6G (Rho6G) and rhodamine 123 (Rho123) show high and moderate affinity to P-gp, respectively. Due to the novelty of this system, the PEG-Rho linker was first assessed in vitro to determine if it was still capable of interacting with P-gp as a substrate. It was evident that the conjugates of PEG-Rho still remained P-gp substrates; therefore, the PLA-PEG nanoparticle was developed to assess targeting of the drug delivery system in vivo. Before targeting efficiency could be measured in vivo a nanoparticle detection method was needed. The autofluorescence of various tissues poses a problem when considering nanoparticle detection by fluorescence in vivo. Therefore, the time resolved fluorescent properties of europium chelates were utilized to overcome autofluorescence challenges. Europium chelates continue to emit photons microseconds after excitation, whereas the autofluorescent molecules in tissues emit photons for only nanoseconds. By measuring photon emittance at microsecond timescales following excitation, the autofluorescent background was eliminated allowing sensitive detection of the nanoparticles in vivo. Once the Rho-PEG-PLA nanoparticle was synthesized and a detection method to track and quantify the particles in vivo was developed, the targeting efficiency of the systems was assessed. In a mouse model, Rho6G-PEG-PLA nanoparticles accumulated 2.6 times greater in the brain than untargeted control mPEG-PLA nanoparticles. Using a P-gp knockout mouse, the accumulation of Rho6G-PEG-PLA nanoparticles was shown to significantly decrease in the brain compared to the wild type mouse. Thus the conclusion was made that Rho6G-PEG-PLA nanoparticles can actively target P-gp at the BBB and can enhance the accumulation of drug delivery nanoparticles in the CNS.

Here is a comprehensive overview of the drugs that act on the central and peripheral nervous systems. This volume thoroughly describes the diseases associated with the nervous system and the drugs used for their treatment while also looking at the current status of these drugs and their future potential and challenges. Divided into three sections, the book first focuses on the drugs that affect the functions of the autonomic nervous system to produce therapeutic effects. These drugs may act presynaptically by manipulating the genesis, storage, and secretion, and by blocking the action of neurotransmitters. Some drugs may trigger or impede postsynaptic receptors. Section 2 focuses on drugs that affect the central nervous system, including antianxiety drugs, sedative and hypnotic drugs, antidepressant drugs, antipsychotic drugs, antiepileptic drugs, and many more. It covers the pharmacological management of various diseases, including Alzheimer's, Parkinson's, Huntington's, and others. The last section offers explanations of neurochemical interactions with the aim to develop drugs that have beneficial effects on neurochemical imbalances. This section demonstrates models to assess the transport of drugs across the blood-brain barrier and nanomedicine to treat brain disorders. This rich compilation provides thorough and extensive research updates on the important advances in neuropharmacological drugs and drug therapy from experienced and eminent academicians, researchers, and scientists from throughout the world.

This timely and compact monograph addresses how to determine drug permeability across the blood-brain barrier more effectively. Focusing on the physiological mechanisms that influence the passage of agents into the brain, the book covers the latest research on the blood-brain barrier, the current problems of and solutions to drug delivery to the central nervous system (CNS), existing strategies, and prospects for future research.Avoid excessive in vivo experimentation and utilize timesaving in vitro techniques. A concise reference with reviews from nearly 40 international specialists in diverse fields, The Blood-Brain Barrier and Drug Delivery to the CNSassesses the properties of the blood-brain barrier to determine and measure drug permeability in animals and humans presents techniques to predict successful drug uptake through in vitro systems or by computation of physicochemical parameters examines the multidrug resistance protein P-glycoprotein as a natural transporter analyzes current drug designs to known requirements for transport looks at drug delivery systems for the brain and much more!Densely packed with over 800 literature references, drawings, photographs, x-rays, tables, and equations, The Blood-Brain Barrier and Drug Delivery to the CNS is a vital addition to the bookshelves of biochemists, pharmacists, clinical and research pharmacologists, neuroscientists and neurologists, and graduate and medical school students in these disciplines.

Drug Delivery Through the Blood-brain Barrier

The Neurology of AIDS

Optimizing Brain Exposure of CNS Drugs and Minimizing Brain Side Effects for Peripheral Drugs

The Cerebral Circulation

Blood-Brain Barrier On-a-chip Model for the Study of Drug Permeability Into the Brain

Drug transport across the blood-brain barrier

This book provides comprehensive information of the nanotechnology-based pharmaceutical product development including a diverse range of arenas such as liposomes, nanoparticles, fullerenes, hydrogels, thermally responsive externally activated theranostics (TREAT), hydrogels, microspheres, micro- and nanoemulsions and carbon nanomaterials. It covers the micro- and nanotechnological aspects for pharmaceutical product development with the product development point of view and also covers the industrial aspects, novel technologies, stability studies, validation, safety and toxicity profiles, regulatory perspectives, scale-up technologies and fundamental concept in the development of products. Salient Features: Covers micro- and nanotechnology approaches with current trends with safety and efficacy in product development. Presents an overview of the recent progress of stability testing, reverse engineering, validation and regulatory perspectives as per regulatory requirements. Provides a comprehensive overview of the latest research related to micro- and nanotechnologies including designing, optimisation, validation and scale-up of micro- and nanotechnologies. Is edited by two well-known researchers by contribution of vivid chapters from renowned scientists across the globe in the field of pharmaceutical sciences. Dr. Neelesh Kumar Mehra is working as an Assistant Professor of Pharmaceutics & Biopharmaceutics at the Department of Pharmaceutics, National Institute of Pharmaceutical Education & Research (NIPER), Hyderabad, India. He received 'TEAM AWARD' for successful commercialisation of an ophthalmic suspension product. He has authored more than 60 peer-reviewed publications in highly reputed international journals and more than 10 book chapter contributions. He has filed patents on manufacturing process and composition to improved therapeutic efficacy for topical delivery. He guided PhD and MS students for their dissertations/research projects. He has received numerous outstanding awards including Young Scientist Award and Team Award for his research output. He recently published one edited book, 'Dendrimers in Nanomedicine: Concept, Theory and Regulatory Perspectives', in CRC Press. Currently, he is editing books on nano drug delivery-based products with Elsevier Pvt Ltd. He has rich research and teaching experience in the formulation and development of complex, innovative ophthalmic and injectable biopharmaceutical products including micro- and nanotechnologies for regulated market. Dr. Arvind Gulbake is working as an Assistant Professor at the Faculty of Pharmacy, School of Pharmaceutical & Population Health Informatics, at DIT University, Dehradun, India. He has authored more than 40 peer-reviewed publications in highly reputed international journals, four book chapters and a patent contribution. He has received outstanding awards including Young Scientist Award and BRG Travel Award for his research. He is an assistant editor for IJAP. He guided PhD and MS students for their dissertations/research projects. He has successfully completed extramural project funded by SERB, New Delhi, Government of India. He has more than 12 years of research and teaching experience in the formulation and development of nanopharmaceuticals.

The Blood Brain Barrier - Regulation of Fatty Acid and Drug Transport.

The development of new CNS drugs is notoriously difficult. Drugs must reach CNS target sites for action and these sites are protected by a number of barriers, the most important being the blood–brain barrier (BBB). Many factors are therefore critical to consider for CNS drug delivery, e.g. active/passive transport across the BBB, intra-brain distribution, and central/systemic pharmacokinetics, to name a few. Neurological disease and trauma conditions add further complexity because CNS barriers, drug distribution and pharmacokinetics are dynamic and often changed by disease/trauma. Knowledge of all these factors and their interplay in different conditions is of utmost importance for proper CNS drug development and disease treatment. In recent years much information has become available for a better understanding of the many factors important for CNS drug delivery and how they interact to affect drug action. This book describes small and large drug delivery to the brain with an emphasis on the physiology of the BBB and the principles and concepts for drug delivery across the BBB and distribution within the brain. It contains methods descriptions for studying drug delivery, routes and approaches of administering drugs into the brain, the influence of disease, drug industry perspectives, and a primer on neuroanatomy and physiological considerations written specifically for drug delivery scientists. Therewith, it contributes to an in-depth understanding of the interplay between brain (patho)-physiology and drug characteristics. Furthermore, the content is designed to be both cutting-edge and educational, so that the book can be used in high-level training of academic and industry scientists with full references to original publications.

Brain Drug Targeting

Drugs and Therapeutics

From Ontogeny to Artificial Interfaces

Blood-Brain Barrier in Drug Discovery

Enabling Novel Treatments for Nervous System Disorders by Improving Methods for Traversing the Bloodâ¬"Brain Barrier

Drug Delivery of Oligonucleotides at the Blood Brain Barrier

The thesis of this innovative and challenging book, first published in 2001, is that brain drug development has been restricted by the failure of adequate brain drug targeting, and that this is an increasingly urgent problem as developments in genomics lead to new generations of therapeutic macromolecules. The author, a world leader in the study of the blood-brain barrier and its clinical implications, reviews the field of neurotherapeutics from the point of view of drug targeting. He surveys the scientific and clinical basis of drug delivery across biological membranes, including topics such as genetically engineered trojan horses for drug targeting, antisense neurotherapeutics, and gene therapy of brain disorders. At a time when there are few significant new drug treatments in prospect for common neurological diseases, this authoritative review will encourage a wide range of clinicians and neuroscientists to reexamine the development and use of drugs in treating disorders of the central nervous system.

Despite substantial advances in developing treatments for the serious illnesses that affect people worldwide, there remains a tremendous unmet need in the treatment of complex neurologic diseases, including neuropsychiatric and neurodegenerative disorders. Chief among the challenges that have hindered the development of therapeutics for central nervous system (CNS) disorders is the blood â €"brain barrier (BBB). The Forum on Neuroscience and Nervous System Disorders of the National Academies of Sciences, Engineering, and Medicine convened a workshop to explore the challenges associated with the BBB that have thus far stymied development of CNS drugs, examine new technologies that could address these challenges, and highlight potential opportunities for moving the field forward. This publication summarizes the presentations and discussions from the workshop.

This e-book will review special features of the cerebral circulation and how they contribute to the physiology of the brain. It describes structural and functional properties of the cerebral circulation that are unique to the brain, an organ with high metabolic demands and the need for tight water and ion homeostasis. Autoregulation is pronounced in the brain, with myogenic, metabolic and neurogenic mechanisms contributing to maintain relatively constant blood flow during both increases and decreases in pressure. In addition, unlike peripheral organs where the majority of vascular resistance resides in small arteries and arterioles, large extracranial and intracranial arteries contribute significantly to vascular resistance in the brain. The prominent role of large arteries in cerebrovascular resistance helps maintain blood flow and protect downstream vessels during changes in perfusion pressure. The cerebral endothelium is also unique in that its barrier properties are in some way more like epithelium than endothelium in the periphery. The cerebral endothelium, known as the blood-brain barrier, has specialized tight junctions that do not allow ions to pass freely and has very low hydraulic conductivity and transcellular transport. This special configuration modifies Starling's forces in the brain microcirculation such that ions retained in the vascular lumen oppose water movement due to hydrostatic pressure. Tight water regulation is necessary in the brain because it has limited capacity for expansion within the skull. Increased intracranial pressure due to vasogenic edema can cause severe neurologic complications and death.

Proceedings of a Workshop

Volume 1 Basic Science Aspects

Nanocarriers for Brain Targeting

Transporters and Drug-Metabolizing Enzymes in Drug Toxicity

Drug Delivery across the Blood – Brain Barrier

Mechanisms and Efficiency

Nanotechnology Methods for Neurological Diseases and Brain Tumors: Drug Delivery across the Blood-Brain Barrier compiles the latest (and future potential) treatment strategies for brain tumors and neurological diseases, in particular Alzheimer ' s, Parkinson ' s and stroke, those that bypass the blood/brain barrier. The current understanding of brain drug delivery and access is discussed in Chapter One, with the next section focusing on the implementation of the nose-to-brain intranasal route in brain-targeted drug delivery. In addition, nanotechnology-based brain drug delivery is covered in Chapter Three. This avenue offers impressive improvement in the treatment of neurological diseases and brain tumors by using bio-engineered systems that interact with biological systems at a molecular level. In Chapter Four, emphasis is placed on the need for brain-targeted experimental models that mimic disease conditions. Final chapters discuss the very latest advances in targeted treatment strategies for neurological diseases and brain tumors. Comprehensive guide for up-to-date views on the latest advances in targeted treatment strategies for brain tumors and neurological diseases Designed with a multidisciplinary approach that links neurology, neuro-oncology and nanoscience to drug delivery to the brain with an emphasis on the blood-brain-barrier Written in a language that makes it easy to understand nanotechnology drug delivery techniques Presents a unique book that also covers advanced treatment approaches of neurological diseases and brain tumors

This book presents a comprehensive collection of current knowledge and leading research about the blood-brain barrier. The chapters are organized in four main parts providing basic information and novel insights about the physiology of the blood-brain barrier, the challenges related to finding and developing drugs crossing the blood-brain barrier, experimental methods to study the blood-brain barrier and the role of the blood-brain barrier in disease mechanisms and its consequences for drug development. In the first part the readers will discover the structure, function and developmental aspects of the blood-brain barrier and gain novel insights into the complexity and functionality of the neurovascular unit and energy metabolism of brain endothelial cells. Chapters of the second part focus on translational challenges from the bench to the bedside in CNS drug development, shed light on the importance to understand the brain distribution of drugs related to their efficacy, elaborate on general pharmacokinetic considerations for CNS drugs and introduce current and novel drug delivery strategies to overcome the blood-brain barrier. The experimental part of the book covers mathematical and in vitro models as well as animal and human methods in blood-brain barrier research. Specific emphasis is set on the description of the methods, the role of species differences for data interpretation, novel human models based on stem cells with the potential for personalized medicine and technical considerations and tips helpful for readers interested in working with these models. In the fourth part particular attentions is given to the blood-brain barrier, its changes and participation during disease progression. Chapters summarize alterations of the blood-brain barrier that are present in common disorders such as Alzheimer ' s disease, multiple sclerosis, stroke, traumatic brain injury, epilepsy and brain tumors. Present therapies will be discussed and the consequences for novel treatment approaches that need to bypass the blood-brain-barrier will be explored. In addition, experts discuss the question in how far changes at the blood-brain barrier are causally linked to disease progressions and consequently could serve as therapeutic targets. This collection is designed to appeal to a wide readership from students through basic and applied scientist to pharmacologists, medical doctors and stakeholders from the pharmaceutical industry and regulatory affairs. Due its comprehensive content the book has the potential to become a standard work in the field of blood-brain barrier research.

Discusses new and established strategies for delivering peptides and antibodies through the blood-brain barrier. It reviews concepts on blood-brain barrier transport biology, assesses the utility and limitations of traditional brain drug delivery methods and describes new drug delivery techniques.

Drug Delivery to the Brain

The Blood-brain Barrier and Drug Delivery of the CNS

Bolavesicles for Drug Delivery Across the Blood-brain Barrier

The Blood Brain Barrier (BBB)

The Future of Brain Drug Development

Physiological Concepts, Methodologies and Approaches

The availability of various in vitro and in vivo techniques has considerably advanced the research on drug transport and metabolism across the blood-brain barrier (BBB). These specialized and sophisticated experimental strategies are of fundamental importance if one is to gain a greater understanding of enhanced and selective drug delivery to the brain. The reader will find in this book methods for in vitro endothelial/astrocyte cell culture models, and for in vivo intracerebral microdialysis to study drug tranport across the BBB. This book, however, is not merely a laboratory manual consisting of recipes for BBB research; it permits the presentation of the different methods in fine detail, revealing tricks and short cuts that frequently do not appear in the literature. The researcher is well aware that differences (subtle or otherwise) in experimental steps used in different laboratories may influence the outcome of any particular procedure. The book also illustrates the accessibility and the application of the different methods in different species. Background information of the protocol is given in every chapter, which also contains a literature list that the reader may wish to refer to for further information. This volume will be invaluable to basic researchers as well as to those involved in the search for agents suitable for pharmaceutic intervention in the central nervous system.

Understanding the structure and function of the blood-brain barrier (BBB) and recogniz ing its clinical relevance require a concert of scientific disciplines applied from a view point of integrative physiology rather than from only molecular or analytical approaches. It is this broad scope that is emphasized in this book. In my opinion, four original contributions define the field as it exists today. The first, a monograph by Broman,1 entitled The Permeability of the Cerebrospinal Vessels in Normal and Pathological Conditions, was the model for many subsequent clinical and 3 experimental studies on BBB pathology. Second, experiments by Davson, summarized in his book entitled Physiology of the Ocular and Cerebrospinal Fluids, indicated that passive entry of nonelectrolytes into brain from blood is governed largely by their lipid 4 solubility. This research supported the original suggestion by Gesell and Hertzman that cerebral membranes have the semipermeability properties of cell membranes. The modern era of the barrier was introduced with the 1965 paper by Crone,2 entitled "Facilitated transfer of glucose from blood to brain tissue. " This paper identified stereospecific, facilitated transport of glucose as part of a system of regulatory barrier properties at a time when only a barrier to passive diffusion had been contemplated. Finally, the 1967 paper by Reese and Kamovsky, 11 entitled "Fine structural localization of a blood-brain barrier to exogenous peroxidase," sited the barrier at the continuous layer of cerebrovascular endothelial cells, which are connected by tight junctions.

Medicinal chemistry is both science and art. The science of medicinal chemistry offers mankind one of its best hopes for improving the quality of life. The art of medicinal chemistry continues to challenge its practitioners with the need for both intuition and experience to discover new drugs. Hence sharing the experience of drug research is uniquely beneficial to the field of medicinal chemistry. Drug research requires interdisciplinary team-work at the interface between chemistry, biology and medicine. Therefore, the topic-related series Topics in Medicinal Chemistry covers all relevant aspects of drug research, e.g. pathobiochemistry of diseases, identification and validation of (emerging) drug targets, structural biology, drugability of targets, drug design approaches, chemogenomics, synthetic chemistry including combinatorial methods, bioorganic chemistry, natural compounds, high-throughput screening, pharmacological in vitro and in vivo investigations, drug-receptor interactions on the molecular level, structure-activity relationships, drug absorption, distribution, metabolism, elimination, toxicology and pharmacogenomics. In general, special volumes are edited by well known guest editors.

The Blood-brain Barrier and Drug Delivery to the Cns

characterization by in vitro and in vivo strategies

Advances in Neuropharmacology

Blood-Brain Barrier

Ligand-mediated Transport of Drug Delivery Devices Across the Blood-brain Barrier

Nanoparticles as Drug Carriers Across the Blood-brain Barrier

This timely and compact monograph addresses how to determine drug permeability across the blood-brain barrier more effectively. Focusing on the physiological mechanisms that influence the passage of agents into the brain, the book covers the latest research on the blood-brain barrier, the current problems of and solutions to drug delivery to the central nervous system (CNS), existing strategies, and prospects for future research. Avoid excessive in vivo experimentation and utilize timesaving in vitro techniques. A concise reference with reviews from nearly 40 international specialists in diverse fields, The Blood-Brain Barrier and Drug Delivery to the CNS assesses the properties of the blood-brain barrier to determine and measure drug permeability in animals and humans presents techniques to predict successful drug uptake through in vitro systems or by computation of physicochemical parameters examines the multidrug resistance protein P-glycoprotein as a natural transporter analyzes current drug designs to known requirements for transport looks at drug delivery systems for the brain and much more! Densely packed with over 800 literature references, drawings, photographs, x-rays, tables, and equations, The Blood-Brain Barrier and Drug Delivery to the CNS is a vital addition to the bookshelves of biochemists, pharmacists, clinical and research pharmacologists, neuroscientists and neurologists, and graduate and medical school students in these disciplines.

This text/reference uses 574 figures and illustrations to help explain the relationships between blood and the cerebrospinal fluid (CSF) and central nervous system (CNS). The authors focus on the interaction of these fluids and the relative importance of the transport mechanisms of hormones from blood to nervous tissue. Carrier-mediated transport of many neuroactive peptides is discussed. Special aspects of the blood-brain barrier are covered in detail. An entire chapter is devoted to the comparative physiology of the CSF and the brain barriers. Physiologists in all fields will have an interest in the updated theories covered in this book.

The vasculature of the central nervous system (eNS) is characterized by the existence of the blood-brain barrier (BBB), which can be regarded as both an anatomical and physiological phenomenon. The BBB is formed by a complex cellular system of endothelial cells, astroglia, pericytes, perivascular macrophages and a basal membrane, although the anatomic substrate of the BBB is the interendothelial tight junctions that form a continuous sealing. The BBB serves as an exquisitely controlled, functional gate to the eNS. It not only protects the brain from agents in the blood that could impair neurological function, but also controls the influx and efflux of numerous substances to maintain proper homeostasis and provide the brain with necessary nutrients. The structural and functional integrity of the BBB was shown to be dramatically altered during various diseases of the eNS, including neoplasia, ischemia, trauma, hypertension, inflammation and epilepsy. Recent years research has partially elucidated the mechanisms underlying the development of some of these brain disorders as well as the pathways used by different pathogens, like bacteria and viruses, to initiate eNS infections. The development of in vitro models of the BBB had instrumental role in the understanding of the involvement of the BBB in the pathogenesis of several eNS diseases. The intimate, functional association between the function of the brain and the activity of the BBB makes the later a target for pharmacological modulation that will expand the therapeutic possibilities for a range of neurological diseases.

Drug Transport and Drug-drug Interactions at the Blood-brain Barrier

Evaluation of Blood-brain Barrier Models for Measurement and Prediction of Brain Drug Penetration

Drug Delivery Through the Blood Brain Barrier

Nanotechnology Methods for Neurological Diseases and Brain Tumors

Exploitation of P-glycoprotein at the Blood Brain Barrier for Targeted Drug Delivery

Bioavailability of Drugs to the Brain and the Blood-brain Barrier

This new volume, Nanocarriers for Brain Targeting: Principles and Applications, covers recent research on brain physiology and the development of drug delivery systems. It explores a diverse variety of strategies that can be employed to achieve drug targeting to the brain. The nanocarriers that are discussed include nanoparticles, vesicular carriers, carriers having carbon as a core constituent, dispersed systems, and more. The inherent anatomy and physiology of the brain renders it different from other organs. The past few decades have witnessed significant research on brain ailments in response to a majority of hospitalizations that occur due to age-related central nervous system disorders. The prevalence of diverse diseases such as Alzheimer ' s disease, Parkinson ' s disease, amyotrophic lateral sclerosis, multiple sclerosis, HIV-dementia, etc., affect about 1.5 billion people globally, which is further anticipated to reach 1.9 billion by the year 2020. Nanocarriers for drug delivery to the brain are seen as one of the answers to this growing problem.

Focused on central nervous system (CNS) drug discovery efforts, this book educates drug researchers about the blood-brain barrier (BBB) so they can affect important improvements in one of the most significant – and most challenging – areas of drug discovery. • Written by world experts to provide practical solutions to increase brain penetration or minimize CNS side-effects • Reviews state-of-the-art in silico, in vitro, and in vivo tools to assess brain penetration and advanced CNS drug delivery strategies • Covers BBB physiology, medicinal chemistry design principles, free drug hypothesis for the BBB, and transport mechanisms including passive diffusion, uptake/efflux transporters, and receptor-mediated processes • Highlights the advances in modelling BBB pharmacokinetics and dynamics relationships (PK/PD) and physiologically-based pharmacokinetics (PBPK) • Discusses case studies of successful CNS and non-CNS drugs, lessons learned and paths to the market

The blood-brain barrier (BBB) is the major site for regulation of molecular traffic between the blood and the central nervous system (CNS). In vitro models of brain endothelium are useful for studying BBB physiology. The present study applied two in vitro BBB models, immortalised rat brain endothelial cells (RBE4), and primary porcine brain endothelial cells (PBECs) to study uptake and permeation of small molecules and macromolecules at the BBB. -- The mechanism(s) involved in adenosine-mediated [3H] glutamate transport were examined. Initial uptake in RBE4 cells showed evidence for activation of Na+-dependent transport via excitatory amino acid transporters (EAATs) involving A2A and A2B receptors, and inhibition of Na+-independent transport via XG- involving A2B receptors. The findings are relevant to regulation of brain glutamate during CNS pathologies. However, no clear modulation was observed in the PBECs under similar conditions. -- The in vitro monocultured PBEC BBB model developed showed restrictive tight junctions (transendothelial electrical resistance, TEER, up to 1133±15 ocm2, n = 3 filter inserts), and functional expression of polarised uptake and efflux transporters. The dynamic range of Papp (propranolol: sucrose), indicator of resolution in drug screening, was improved from 2.3 to 57.6 (Papp propranolol 49 x 10-6cm/s; sucrose 0.85 x 10-6cm/s). Application of the model to assay antiepileptic drugs showed no detectable substrate recognition by P-glycoprotein. pCEL-X software (pION INC., Woburn USA) was applied for aqueous boundary layer correction and detailed permeability data analysis to derive intrinsic transcellular permeability Po ;in vitro-in vivo PQ correlation gave r2 = 0.62 for n = 20 compounds. Co-culture of the PBECs with astrocytes gave higher TEER, and functional transcytosis, evidence for upregulation of BBB phenotype. Properties of macromomolecular permeation suggested involvement of the glycocalyx as filtration site-barrier.

Micro- and Nanotechnologies-Based Product Development

Polymeric Vesicles for Drug Delivery Over the Blood-brain Barrier and in Vivo Imaging

The Blood Brain Barrier - Regulation of Fatty Acid and Drug Transport

Physiology of the CSF and Blood-Brain Barriers

Relevance to CNS Drug Delivery

Blood-brain Barrier Permeability and Transport Studied in Vitro

This book provides a comprehensive and up-to-date coverage of the relationship between drug metabolism enzymes and transporters on drug toxicity, along with methods to investigate their role on adverse drug reactions. Unites both the metabolism and transporter components of drug toxicity – two aspects not normally connected and the latter often neglected Familiarizes readers with the mechanism and species differences in drug metabolizing enzymes and transporters Discusses promising approaches to accurately predict human drug toxicity via the incorporation of human drug metabolism in toxicity evaluation

From basic science to clinical care, to epidemiological disease patters, The Neurology of AIDS is the only complete textbook available on AIDS neurology and the only one comprehensive enough to stand alone in each segment of study in brain disorders affected by the human immunodeficiency virus. It is an indispensable resource for students, resident physicians, practicing physicians, and for researchers and experts in the HIV/AIDS field. Oxford Clinical Neuroscience is a comprehensive, cross-searchable collection of resources offering quick and easy access to eleven of Oxford University Press's prestigious neuroscience texts. Joining Oxford Medicine Online these resources offer students, specialists and clinical researchers the best quality content in an easy-to-access format.

This new volume of Advances in Pharmacology presents pharmacology of the blood brain barrier, focusing on targeting CNS disorders. With a variety of chapters and the best authors in the field, the volume is an essential resource for pharmacologists, immunologists and biochemists alike. Contributions from the best authors in the field An essential resource for pharmacologists, immunologists, and biochemists

Principles and Applications

Drug Transport Across the Blood-brain Barrier

Implications of the Blood-Brain Barrier and Its Manipulation

Drug Delivery and Brain Pathology

A Therapeutic Strategy for Inflammatory Diseases of the Central Nervous System

Physiology, Pharmacology and Pathology of the Blood-Brain Barrier

This is the first handbook to integrate developmental and cellular aspects combining the different structural and functional features involved in the regulation of brain perfusion and neuronal function. It highlights pharmacological and biomedical applications with sections on drug delivery and disease-related states as well as explaining in detail the role of astrocytes, shown to be an essential link between neurons and cerebral blood vessels. In addition the book studies how the structural elements interact in response to the dynamics of neuronal activities, necessitating adaptive mechanism of the interface. A significant part of the book describes new approaches to how the barrier can be surmised for drug delivery and how it can be mimicked by artificial in vitro systems for drug testing. Finally, the involvement of the barrier in brain diseases is considered, focusing on inflammatory and neurodegenerative disorders of the brain. Covering basic knowledge as well as specific information dealing with very recent progress in blood-brain interface research, this book is of interest to neurobiologists, neurologists, biochemists, and pharmacologists.

This volume focuses on experimental research with applicable models to study physiology, biochemistry, and molecular biology of the blood-brain barrier (BBB). This book is organized into six parts: Part One is an overview of the physiology of BBB; Part Two explores in vitro cell models to study the BBB; Part Three discusses techniques in vivo and ex vivo models to evaluate BBB in Drosophila melanogaster, Zebrafish, and rodents; Part Four looks at permeability, influx, efflux transportation, and drug delivery through the BBB; Part Five talks about various invasive and non-invasive imaging techniques to study BBB; and Part Six describes how molecular biomarkers are used to look at the integrity or dysfunction of the BBB. In Neuromethods series style, chapters include the kind of detail and key advice from the specialists needed to get successful results in your laboratory. Cutting-edge and thorough, Blood-Brain Barrier is a valuable resource to aid both novice and experienced investigators with performing experiments using new and classic translational approaches.

Playing an important role in the treatment of neurological disorders, the delivery of drugs to central nervous system (CNS), both administered directly and administered systematically for targeted action, encounters a major challenge in the form of the blood-brain barrier (BBB), which limits the access of drugs to the brain substance. In Drug Delivery to the Central Nervous System, experts in the field present essential methods used to deliver therapeutics across the BBB, both in experimental animals and in humans. In addition to those methods, several overviews of innovative methods and their applications are presented in order to give a glimpse of the future of this research. As a volume in the successful Neuromethods series, this book presents its protocols with the kind of detailed description and implementation advice that is crucial for getting optimal results. Authoritative and cutting-edge, Drug Delivery to the Central Nervous System serves as an ideal guide to scientists continuing to pursue knowledge of the delicate interactions between pharmaceuticals and the brain.

Peptide Drug Delivery to the Brain

Blood-Brain Barriers

Pharmacology of the Blood Brain Barrier: Targeting CNS Disorders

In vitro and In vivo Techniques

Drug Delivery to the Central Nervous System

Technical Review Meeting on "Drug Bioavailability and the Blood-brain Barriers" : Papers