



# Transport of Amino Acids Across the Blood-Brain Barrier

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The blood-brain-barrier (BBB), present in brain capillaries, constitutes an essential barrier mechanism for normal functioning and development of the brain. The presence of tight junctions between adjacent endothelial cells restricts permeability and movement of molecules between extracellular fluid and plasma. The protein complexes that control cell-cell attachment also polarize cellular membranes, so that it can be divided into luminal (blood-facing) and abluminal (brain) sides, and each solute that enters/leaves the brain must cross both membranes. Several amino acid (AA) transport systems with different distributions on both sides of the BBB have been described. In a broad sense, there are at least five different systems of facilitative transporters and all of them are found in the luminal membrane. Some of these transporters are very specific for a small group of substrates and are located exclusively on the luminal side of the BBB. However, the two major facilitative carriers, system L and system y<sup>+</sup>, are located in both membranes, although asymmetrically. The position of these Na<sup>+</sup>-independent transporters ensures AA availability in the brain and also its bidirectional transport across the endothelial cells. On the other hand, there are several Na<sup>+</sup>-dependent transport systems that transport AAs against its concentration gradient together with the movement of Na<sup>+</sup> ions. The majority of these active transporters are present exclusively at the abluminal membrane and are responsible for AA efflux from the brain into the endothelial cells. Since they are Na<sup>+</sup>-coupled, the sodium pump Na<sup>+</sup>/K<sup>+</sup>-ATPase is also highly expressed on this abluminal side of the BBB. Once inside the cell, the facilitative transporters located in the luminal membranes mediate export from the endothelial cell to the blood. In summary, the polarized distribution of these transport systems between the luminal and abluminal membranes, and the fact that more than one transporter may carry the same substrate, ensures supply and excretion of AAs in and out of the brain, thereby controlling its homeostasis and proper function.

**Keywords:** blood-brain barrier, amino acid transport, facilitative transport, active transport, cell polarity, luminal membrane, abluminal membrane, endothelial cells

## INTRODUCTION

### The Blood Brain Barrier

The term blood-brain barrier (BBB) was used to describe the unique characteristics of the microvasculature of the central nervous system (CNS). Such vessels within the CNS are continuous and non-fenestrated capillaries; moreover, endothelial cells (ECs) within the BBB are held together by continuous interendothelial tight junctions that limit paracellular transport across the

# Blood Brain Barrier Amino Acids

**Frade Fonnum**



## **Blood Brain Barrier Amino Acids:**

*The Blood-Brain Barrier, Amino Acids and Peptides* M. Segal, Berislav V. Zlokovic, 2012-12-06

Definition of the barrier The interstitial fluid rSF of the brain is separated from the blood by the blood brain barrier BBB This barrier must not be thought of as a single entity or as an absolute restriction to all molecules but as a multiple structure located at several sites within the brain The first of these interfaces is located at the endothelium of the brain capillaries Secondly there is a potential site for interchange on the outer linings of the brain between the dura and the arachnoid membranes Thirdly there are the choroid plexuses and the cerebrospinal fluid CSF which is in contact with the very permeable internal ependymal lining of the brain Figure 1 1 Finally there are areas of the brain which lack a blood brain barrier These areas constitute the circumventricular organs and have leaky capillaries with a barrier at the ependyma which limits the spread of molecules from those regions Figure 1 2 Each of these BBB sites has its own characteristic permeability and transport functions We will now consider the properties of each of these barrier sites between the blood and the brain

### **THE CEREBRAL CAPILLARY ENDOTHELIUM**

**Morphology** This interface has both the largest surface area and the shortest path length between the blood and the brain rSF The cerebral capillaries which at first sight seem little different from the rest of the systemic circulation are in fact unique to the brain

### **Peptide and Amino Acid Transport Mechanisms in the Central Nervous System**

Ljubiša Rakić, 1988 Addresses the regulation within the brain extracellular fluid of peptide and amino acid levels particularly neurotransmitters and neuromodulators Particular attention is devoted to the way in which peptides may either penetrate the blood brain barrier or alter its permeability to other solutes Focuses on central nervous system disease especially in designing drugs and agents which will penetrate the blood brain barrier and exert central nervous actions

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### Amino Acid Availability and Brain Function in Health and Disease

Gerald Huether, 2013-06-29 The picture on the following page is being reproduced here at the request of the participants in the Advanced Research Workshop Amino Acid Availability and Brain Function in Health and Disease I displayed this limewood carving entitled Neurochemistry during my closing remarks to this extraordinarily stimulating and productive workshop so ably organized by my collaborator Dr Gerald Huether We scientists need two sturdy legs to carry us through all the twists and turns of our academic careers We should also have as it were a reserve leg handy to help us stay upright when this career ends My third leg is wood carving The idea for Neurochemistry came to me in the plane carrying me to the congress of the International Neurochemical Society in Jerusalem We need the hands for our meticulous experimental work and at least one ear to listen to the messages our neurons send us A few years ago it would have been premature to hold a workshop on this subject Now however the time was just right to allow an overview of the status of current research and to point out the promising new openings it has created There is no doubt that the book to be published as a result of this workshop will be for the next years at least the standard text on the subject Hearty thanks to all speakers for their brilliant

contributions and to all participants for the lively uninhibited and stimulating discussion

*Amino Acids as Chemical Transmitters* Frade Fonnum, 2012-12-06 This volume represents the proceedings of a NATO Advanced Study Institute on Amino Acids as Chemical Transmitters which took place at Spatind Hotel in Norway August 14-21 1977 The meeting is related to two previous meetings on metabolic compartmentation in the brain The first of these meetings took place at Rockefeller Foundation Bellagio Italy July 11-16 1971 and the proceedings *Metabolic Compartmentation in Brain* were edited by R Balazs and J E Cremer and published by Macmillan in 1973 The second meeting was an Advanced Study Institute on Metabolic Compartmentation and Neurotransmission Relation to Brain Structure and Function which was held in Oxford September 1-8 1974 The proceedings were edited by S Berl D D Clarke and D Schneider and published as Volume 6 of the NATO ASI Life Science series by Plenum Press The object of the present meeting was to review and discuss the present status of amino acids as chemical transmitters Several issues such as electrophysiological response localization synthesis release and receptor binding of transmitter candidates were discussed The possible morphological correlates to these functions were also reviewed During the meeting 24 leading papers were given In addition several of the participants presented important new findings during the discussion Some of these have been included as short reports The main financial support was obtained from NATO Scientific Affairs Division

*Radiopharmaceuticals and Brain Pathophysiology Studied with PET and SPECT* M. Diksic, Richard C. Reba, 2021-09-28 First published in 1991 this book covers three major areas essential to in vivo biochemical studies with PET and SPECT synthesis of radiopharmaceuticals biological modeling and clinical applications The book emphasizes advances in the synthesis of radiopharmaceuticals used in PET and SPECT studies of brain flow and oxidative metabolism in addition to biological modeling The most widely used 2 deoxyglucose 2 fluorodeoxyglucose models are discussed as well as models used in the quantitation of brain receptors Other topics include a possible model for converting 6 18F fluorodopa images into the quantitative rate of dopamine synthesis evaluations of technetium and iodine labeled blood flow tracers and possibilities for using SPECT to measure other pathophysiological variables This book will be a valuable reference source to students and specialists interested in these in vivo measurements

**Barriers and Fluids of the Eye and Brain** Malcolm Beverley Segal, 1992 This volume presents the latest findings regarding the control of the fluid environments of the eye and brain The book is comprised of papers presented at a symposium honoring the 80th birthday of Professor Hugh Davson The contributors are previous students of Hugh Davson who are now leading authorities in the fields of the eye and brain The eye is considered from its many interfaces including the role of prostaglandins blood flow in diabetes and the vitreous body Other topics discussed include the role of carbonic anhydrase cerebrospinal fluid and its drainage and the development of the blood brain barrier to macromolecules The book also shows how recent findings about homologous molecules refute earlier studies with foreign tracers and offers a fascinating glimpse into the future with a description of the latest imaging techniques used in neurological diagnosis

**Neurobiology of Cerebrospinal Fluid 1**

James H. Wood, 2013-06-29 Physiologic compartmentalization effectively isolates the central nervous system from the rest of the body. This isolation not only provides protection of its delicate function from aberrant peripheral influences but also impedes its diagnostic evaluation. Cerebrospinal fluid (CSF) bathes the brain and spinal cord and is in dynamic equilibrium with its extracellular fluid and tends to reflect the state of health and activity of the central nervous system. CSF examination is the most direct and popular method of assessing the central chemical and cellular environment in the living patient or mammal. The purpose of this multidisciplinary reference text is to provide the sophisticated knowledge of CSF physiology and pathology necessary for the meaningful interpretation of data obtained by various types of CSF analysis. The methodology for reliable CSF collection, storage, preparation and analysis is discussed with respect to individual somatotropic, chronologic, endocrinologic, pharmacologic and possible artifactual variations in CSF composition. These essential aspects which ensure the validity of CSF data are presented to aid the investigator in clinical and experimental protocol formulation and in elimination of possible sources of error.

*Regulatory Mechanisms of Neuron to Vessel Communication in the Brain*

Fiorenzo Battaini, Stefano Govoni, Maria S. Magnoni, Marco Trabucchi, 2013-06-29 Proceedings of the NATO Advanced Research Workshop on Regulatory Mechanisms of Neuron to Vessel Communication in the Brain held in Salo, Italy, September 3-8, 1988.

Fuel Homeostasis and the Nervous System

Mladen Vranic, Suad Efendic, Charles H. Hollenberg, 2012-12-06 This book has a dual purpose: to review in depth the control of fuel homeostasis in the brain and the role of the nervous system in the control of fuel deposition in the body. From the methodological point of view, the emphasis is on the application of advanced technologies to assess fuel transport and brain metabolism, the role of peptides in the neuroendocrine system and the response of the brain to hypoglycemia. These technologies include positron emission tomography, nuclear magnetic resonance, immunocytochemistry, molecular biology, autoradiography. To study fuel homeostasis in the body, advanced tracer methods that include modelling are set out. From the pathophysiological point of view, the emphasis is on abnormalities in stress, brain metabolism in diabetes, eating and degenerative disorders. This book contains contributions from endocrinologists, physiologists, neurologists, psychoneuroendocrinologists, biophysicists, biochemists and experts in nutrition. This authorship represents a unique diversity of researchers who for the first time comprehensively cover the interaction between the nervous system and fuel homeostasis both in health and disease. We hope this book will be an important source of information for both researchers and practicing clinicians.

Mladen Vranic, Suad Efendic, Charles Hollenberg v  
ACKNOWLEDGEMENTS The Symposium from which this volume arose, University of Toronto, June 27-28, 1990, was the first Toronto-Stockholm symposium on Perspectives in Diabetes Research. These Symposia are organized triennially by the Banting and Best Diabetes Centre, University of Toronto and the Department of Endocrinology, Karolinska Institute, Stockholm.

*Principles of Pharmacology* David E. Golan, 2008 This primary textbook for a first course in pharmacology offers an integrated, systems-based and mechanism-based approach to understanding drug therapy. Each chapter focuses on a target

organ system begins with a clinical case and incorporates cell biology biochemistry physiology and pathophysiology to explain how and why different drug classes are effective for diseases in that organ system Over 400 two color illustrations show molecular cellular biochemical and pathophysiologic processes underlying diseases and depict targets of drug therapy Each Second Edition chapter includes a drug summary table presenting mechanism clinical applications adverse effects contraindications and therapeutic considerations New chapters explain how drugs produce adverse effects and describe the life cycle of drug development The fully searchable online text and an image bank are available on thePoint Frontiers in Cerebral Vascular Biology Lester R. Drewes, A. Lorris Betz, 2012-12-06 During the past three decades the cerebral vasculature and its role in blood brain transport has been an increasingly active area of investigation and learning particularly from an anatomical and physiological point of view However much less is known at the molecular and cellular level about the blood brain barrier especially regarding the macromolecules responsible for transport the roles played by vascular wall components endothelial cell pericyte smooth muscle basement membrane and the mechanisms regulating brain vascular specific protein expression and their molecular alterations during development and disease Fundamental questions still unanswered include What are the molecular constituents of brain endothelial cell tight junctions What are the membrane proteins responsible for transport of specific substrates What are the molecular signals that cause glucose transporter gene expression to be 20 to 100 times greater in brain endothelial cells in vivo than in vitro What roles do pericytes smooth muscle cells and basement membrane have in establishing or maintaining blood brain transport characteristics Are brain vascular transport systems responsible for edema following injury Are transporter systems regulated via receptor mediated events Do hormones or neuromodulators regulate transporter expression What is the molecular mechanism by which plasma proteins enter the extravascular space Are transporters asymmetrically distributed between the luminal and abluminal endothelial cell membranes Can prodrugs or pharmacologic agents be designed as substrate analogs and be delivered to the central nervous system via existing transporters or receptors Can new and beneficial transporters be introduced into the brain vasculature

*Dietary Phenylalanine and Brain Function* WURTMAN, RITTER-WALKER, 2012-12-06 This volume contains the manuscripts of the full papers and posters presented at the conference Dietary Phenylalanine and Brain Function which took place at the Park Hyatt Hotel Washington D C on May 8 10 1987 The conference was organized by a committee that included Drs Louis Elsas Emory University Atlanta William Pardridge UCLA Timothy Maher Massachusetts College of Pharmacy Donald Schomer Harvard and Richard Wurtman MIT It was sponsored by the Center for Brain Sciences and Metabolism Charitable Trust a foundation which during the past few years had also organized seven other conferences related to interactions between circulating compounds drugs nutrients hormones toxins and brain function The Center's most recent other conferences were on Melatonin in Humans Vienna Austria November 1985 and The Pharmacology of Memory Disorders Associated with Aging Zurich Switzerland January 1987 The decision to organize this conference was based on the

perception that major changes had recently occurred in society's uses of phenylalanine and phenylalanine containing products and on the belief that a meeting of scientists and physicians who work on the amino acid's neurological effects could both catalyze additional research on these effects and assist regulatory bodies in formulating appropriate public policies relating to the use of these products phenylalanine in both its L and D forms has apparently become a popular sales item at health food stores and thus is now being consumed by a fairly large number of people in the absence of the other

Amino Acid Transport Across the Murine Blood-brain Barrier Nadine Ruderisch, 2010 *Intramural Annual Report*  
National Institute on Aging, 1990 **Annual Report** National Institute on Aging, 1987 **Pharmacogenomics** Julio Licinio, Ma-Li Wong, 2009-07-30 This work represents the first comprehensive publication in the innovative field of pharmacogenomics a field which is set to revolutionize pharmaceutical research In addition to renowned editors the list of contributors is a who is who in the field Broad coverage of all aspects of pharmacogenomics with a full presentation of applications to disease conditions is featured Anyone involved in pharmaceutical research and drug development needs this book to keep up with this new and revolutionary approach *Cumulated Index Medicus*, 1975 *Cirrhosis, Hepatic Encephalopathy, and Ammonium Toxicity* Santiago Grisolia, Vicente Felipo, Maria-Dolores Miñana, 2013-03-08 Proceedings of an international symposium held in Valencia Spain November 27-29 1989 **Nutrient Metabolism** Martin Kohlmeier, 2003-10-01 Nutrient Metabolism defines the molecular fate of nutrients and other dietary compounds in humans as well as outlining the molecular basis of processes supporting nutrition such as chemical sensing and appetite control It focuses on the presentation of nutritional biochemistry and the reader is given a clear and specific perspective on the events that control utilization of dietary compounds Slightly over 100 self contained chapters cover all essential and important nutrients as well as many other dietary compounds with relevance for human health An essential read for healthcare professionals and researchers in all areas of health and nutrition who want to access the wealth of nutrition knowledge available today in one single source Key Features Highly illustrated with relevant chemical structures and metabolic pathways Foreword by Steven Zeisel Editor in chief of the Journal of Nutritional Biochemistry First comprehensive work on the subject **Carbohydrate and Glycoprotein Metabolism; Maternal Phenylketonuria** R. Angus Harkness, R.J. Pollitt, G.M. Addison, 2012-12-06 394 finding by Dr C Jakobs Amsterdam was elevated plasma galactitol and or sorbitol levels in some cataract patients with quite normal activities of the galactose degrading enzymes and sorbitol dehydrogenase in RBC Inherited disorders of glycoprotein metabolism were reviewed by Dr M Cantz Heidelberg followed by detailed presentations on selected disorders The meeting was closed by two exciting lectures given by Dr J R Hobbs London and Dr F Ledley Houston on the outcome of bone marrow transplantation and on future aspects of gene therapy in patients with inborn errors of metabolism Each year the Mini Symposium preceding the main topics attracts increasing numbers and in Munich more than half of the 281 active participants also attended on Maternal Phenylketonuria organized by Dr the highly interesting

workshop D Brenton London This four hour workshop included international practical experiences in the treatment of maternal phenylketonuria as well as the results of amino acid transport and animal experiments



## Whispering the Strategies of Language: An Mental Journey through **Blood Brain Barrier Amino Acids**

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