

Structural Insight into the Aromatic Amino Acid Hydroxylases and Their Disease-Related Mutant Forms

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1. Introduction

The mammalian aromatic amino acid hydroxylases (phenylalanine, tyrosine, and tryptophan hydroxylase (PheOH, TyrOH, TrpOH, respectively)) are functionally and structurally closely related enzymes (e.g. 65% sequence identity and 80% sequence homology

in the catalytic domains)¹ (Figure 1). This family of enzymes shares a common catalytic mechanism, in which dioxygen is used by an active site containing a single, reduced iron atom to hydroxylate an unactivated aromatic substrate (i.e., monooxygenase activity), concomitant with a two-electron oxidation of tetrahydropterin cofactor to its quinonoid dihydropterin form (Figure 2).² The enzymes play an important role in mammalian metabolism: PheOH initiates the catabolism/detoxification of high levels of phenylalanine, while TyrOH and TrpOH catalyze the rate-limiting steps in the biosynthesis of the neurotransmitters/hormones dopamine/noradrenaline/adrenaline and serotonin, respectively. In 1959, Kaufman³ related a deficiency in hPheOH to the genetic disease phenylketonuria (PKU), and more recently a deficiency in hTyrOH has been related to the genetic disease L-DOPA responsive dystonia⁴ and juvenile parkinsonism.⁵ Current research is close to linking TyrOH with bipolar affective disorder⁶ and studying the relationship between DNA polymorphism of the TyrOH gene and schizophrenia⁷ (see section 4). Reduced biosynthesis of L-DOPA by TyrOH as a result of progressive degeneration of dopaminergic neurons in the nigrostriatal pathway is characteristic of idiopathic parkinsonism (Parkinson's disease), and evidence has recently been presented that the TyrOH enzyme system itself may contribute to the oxidative stress considered to be responsible for the neurodegeneration.⁸ While the enzymes operate on different amino acid substrates, the similarity of substrate structure is apparent, and recent data have provided important sequence and mechanistic links between the different hydroxylases.

In solution, the aromatic amino acid hydroxylases form homotetramers with molecular mass ranging from 204 to 217 kDa. Sequence homologies, site-directed mutagenesis, and partial proteolysis experiments have demonstrated that these enzymes are composed of an N-terminal region (PheOH 1-142; TyrOH 1-155; TrpOH 1-177) with regulatory properties and a C-terminal region (PheOH 143-452; TyrOH 156-498; TrpOH 178-445) known to be

* Corresponding author.

Aromatic Amino Acid Hydroxylases And Mental Disease

John Dobbing



Aromatic Amino Acid Hydroxylases And Mental Disease:

Aromatic Amino Acid Hydroxylases and Mental Disease M. B. Youdim, **Aromatic Amino Acid Hydroxylases and Mental Disease** Moussa B. H. Youdim, 1979 **Neurobiology of Mental Illness** Dennis S. Charney, Joseph D. Buxbaum, Pamela Sklar, Eric J. Nestler, 2013-07-04 Our understanding of the neurobiological basis of psychiatric disease has accelerated in the past five years The fourth edition of *Neurobiology of Mental Illness* has been completely revamped given these advances and discoveries on the neurobiologic foundations of psychiatry Like its predecessors the book begins with an overview of the basic science The emerging technologies in Section 2 have been extensively redone to match the progress in the field including new chapters on the applications of stem cells optogenetics and image guided stimulation to our understanding and treatment of psychiatric disorders Sections 3 through 8 pertain to the major psychiatric syndromes the psychoses mood disorders anxiety disorders substance use disorders dementias and disorders of childhood onset Each of these sections includes our knowledge of their etiology pathophysiology and treatment The final section discusses special topic areas including the neurobiology of sleep resilience social attachment aggression personality disorders and eating disorders In all there are 32 new chapters in this volume including unique insights on DSM 5 the Research Domain Criteria RDoC from NIMH and a perspective on the continuing challenges of diagnosis given what we know of the brain and the mechanisms pertaining to mental illness This book provides information from numerous levels of analysis including molecular biology and genetics cellular physiology neuroanatomy neuropharmacology epidemiology and behavior In doing so it translates information from the basic laboratory to the clinical laboratory and finally to clinical treatment No other book distills the basic science and underpinnings of mental disorders and explains the clinical significance to the scope and breadth of this classic text The result is an excellent and cutting edge resource for psychiatric residents psychiatric researchers and doctoral students in neurochemistry and the neurosciences *Amino Acids in Health and Disease* Seymour Kaufman, 1987 *Pathological Neurochemistry* Abel Lajtha, 2013-03-14 More than for any other volume of the Handbook of Neurochemistry the chapters in this volume on Pathological Neurochemistry deal with the interface of the laboratory bench with the patient's bedside Most of the chapters reflect the confluence of basic scientists clinical investigators and physicians Considered here are many of the more important disorders that afflict the nerves muscles spinal cord and or brain of mankind throughout the world There are well over 500 such disorders And our understanding of their nature and of measures for effective prevention or treatment depends significantly on application of the biochemical disciplines that characterize neurochemistry Before World War II any attempt to compile a volume on pathological neurochemistry would have been largely descriptive and very rudimentary as such handbooks by Hans Winterstein 1929 Irvine Page 1937 and others demonstrate But thanks to the many major advances in research and technology in the postwar decades we now stand at the threshold of understanding how to manage many of the major neurological disorders and we may expect more

such delineations in the immediate decades ahead Neurochemistry defined broadly has played a central role in this extraordinary turn of events progressing from what J L W Thudichum in 1884 called objects of anxious empiricism to his anticipation of the proud exercise of chemical precision Handbook of the Biology and Pathology of Mental Disorders Colin R. Martin, Victor R. Preedy, Vinood B. Patel, Rajkumar Rajendram, 2025-08-30 Mental health disorders affect emotions behavior and thought processes which impact on the day to day functioning and well being of the individual and the family unit The consequences can be devastating and should be placed in the context that globally there are approximately 800 million people who have a mental health disorder of which approximately 500 million have either depression or anxiety Approximately 45 million people have bipolar disorder and 20 million have schizophrenia Eating disorders affects 15 million people Substance use disorders affects nearly a billion people worldwide In many cases treatment can be carried out using pharmacological and nonpharmacological regimens However it is important to consider that the biological and pathological elements of these mental disorders are often overlooked understanding which platforms for diagnosis and treatments This comprehensive reference covers the full range of psychological disorders examining the biological aspects of what is displayed as behavior Each major psychological disorder receives its own chapter with information on genetic chemical and biological components that are key factors in the etiology and course of the pathology The interrelationship of human behavior and physical health is a complex but critical part of understanding the mental condition and this reference lays out a way of understanding the role of the biological mechanisms This handbook is designed for psychologists psychiatrists judicial professionals behavioral scientists pathologists psychologists psychiatric nurses and doctors neurologists health scientists general practitioners research scientists and all those interested in altered behavior mental health and disease It is also valuable as a personal reference book and for academic libraries that cover behavioral or medical sciences Hepatic Encephalopathy Roger F. Butterworth, Gilles Pomier Layrargues, 2012-12-06 Rosenberg's Molecular and Genetic Basis of Neurological and Psychiatric Disease, Seventh Edition Roger N. Rosenberg, Juan M. Pascual, 2024-10-04 Rosenberg s Molecular and Genetic Basis of Neurologic and Psychiatric Disease Seventh Edition provides a comprehensive introduction and reference to the foundations and key practical aspects relevant to neurologic and psychiatric disease This volume has been thoroughly revised and includes newly commissioned chapters on ethics genetic counselling and genet therapy for the central nervous system disorders A favorite of over four generations of students clinicians and scholars this new edition retains and expands the informative concise and critical tone of the previous edition This is an essential reference for general medical practitioners neurologists psychiatrists geneticists and related professionals and for the neuroscience and neurology research community at large Both volumes combined provide a comprehensive coverage on the neurogenetic foundation of neurological and psychiatric disease This volume provides a detailed introduction on both the clinical and basic research implications of molecular and genetics surrounding the brain Includes new chapters on genomics of human neurological

disorders CRISPR and genome engineering *Brain, Behaviour, and Iron in the Infant Diet* John Dobbing, 2013-12-14 Iron deficiency in infancy is very widespread even in developed countries and even when there is no general malnutrition This book examines the question whether iron deficiency in early life leads to deleterious changes in brain and or behavioural development Each of the nine contributors comments critically on each of the other eight chapters so that the book is very extensively peer reviewed The evidence is set out so that the reader may make his own informed judgement Iron deficiency could very easily be prevented this fact is of prime importance if such deficiency has long lasting effects on human intellectual capacity and achievement **Organic Acids in Man** R. Chalmers, 2012-12-06 The writing of this book was

prompted by the need for a comprehensive of current data on organic acids suitable for both newcomers and collection established researchers in this field The only previous text of the kind was the excellent review by Nordmann and Nordmann 1961 and at that time the main method of analysis was paper chromatography with liquid chromatography being used in a limited way Only three diseases in which organic acids accumulate were known primary hyperoxaluria phenylketonuria and alcaptonuria Since then with the development of gas chromatography and mass spectrometry and the further development of liquid chromatography knowledge concerning the nature of the organic acids in physiological fluids has been greatly extended At the same time the number of organic acidurias has increased dramatically there being now some 40 50 known diseases of this type During the past 15 years or so there have been several reviews dealing with either specific diseases or groups of diseases Gompertz 1972 1974 Tanaka 1975 or presenting the proceedings of symposia Stern and Toothill 1972 or workshops Marner et al 1974 This present text deals comprehensively and in detail with the organic acids in human physiological fluids in health and in disease states and is particularly concerned with the methods necessary for their separation determination and identification **The Changing Nervous System** Sarah H. Broman, Jack M.

Fletcher, 1999-07-15 This book provides an integrated review of current research on neural plasticity and reorganization after early cerebral insults Addressing both animal studies and a variety of diverse clinical populations including children with congenital brain malformations focal lesions autism and pervasive developmental disorders this book summarizes many of the major advances on neural plasticity made in these areas over the past several years Characterized by a broad historical perspective including contributions from some of the earliest researchers on environmental factors and brain organization the book advances the reader from the laboratory to application in several human populations Many of the components of the book explicitly address relationships of animal and human models showing that the laboratory and the clinic are overlapping settings not isolated chambers as they are often perceived The understanding of neural plasticity and both biological and environmental factors that influence brain reorganization after early cerebral insult has major implications for treatment The book outlines many of the potential applications for treatment of early brain disorders The contributors include basic neuroscientists cognitive neuroscientists and clinician researchers who work together to bridge gaps among disciplines The

book should facilitate collaborative research and applications in the critical areas of neural plasticity and brain reorganization Advancement of knowledge of factors that prevent and enhance brain reorganization after early cerebral insult is a key to unraveling the mysteries of the developmental disorders characteristic of children and which influence their development through adulthood Depressive Illness J. Mendlewicz,A. Coppen,H. M. van Praag,1981-12-15 **The Enzymes** ,1987-03-19 The Enzymes **The Physiology of Psychological Disorders** James G. Hollandsworth Jr.,2013-11-11 Explanations of abnormal behavior that emphasize the importance of physiological determinants of disorder are relatively unpopular among psychologists especially among those who work as clinicians in an applied setting The reasons for this are theoretical and historical as well as practical Physiology and its associated biological disciplines of biochemistry pharmacology and genetics are traditionally more associated with medicine their use to underpin explanations and treatments of behavioral abnormality has consequently demanded knowledge to which most psychologists are not exposed and skills that are unavailable to them The dichotomy thus created between medical and psychological approaches has caused many psychologists to disregard physiological factors Even when the latter are recognized as important many psychologists have been unwilling to admit to the fact in the belief that by doing so they will commit themselves to an overly medical model of psychological disorder undermining what they see as preferred views of abnormality As I have become increasingly aware in following the progress of this book in the United States the theoretical issues in this debate have been further sharpened by professional rivalries present but less explicit on the European scene from which I write between medical and nonmedical health care workers regarding facilities for and approaches to the treatment of the mentally disturbed Faced with these divisions of interest psychologists have available two courses of action *The Enzymes* Paul D. Boyer,1970 *The Molecular and Genetic Basis of Neurologic and Psychiatric Disease* Roger N. Rosenberg,2003 Inside the third edition of this reference the reader will find thorough and authoritative discussions of all of these developments and their implications for clinical practice It includes a major new section on Psychiatric Diseases descriptions of the molecular and genetic basis of the spongiform encephalopathies as well as the expression of the prion gene under physiologic and pathologic conditions additional coverage examines the human genome project and neurologic disease and coverage on alzheimer s disease and related dementias **Central Neurotransmitter Turnover** C. J. Pycock,P. V. Taberner,2012-12-06 The concept of chemical transmission in the central nervous system has taken some time to be generally accepted but an increasing number of compounds are now being recognized as having a transmitter role in the brain The acetylcholine system was the first to be discovered in the periphery and its characteristic features of storage of transmitter in vesicles in the nerve terminal its electrically evoked release and rapid extra neuronal breakdown were considered to be necessary criteria for any neurotransmitter candidate The subsequent elucidation of the noradrenergic system made it apparent that rapid enzymatic breakdown was not essential for a released transmitter and the possibility of high affinity re uptake

processes became established as an alternative means of terminating the synaptic actions of a transmitter. With the eventual acceptance of the amino acids as excitatory or inhibitory transmitters, the requirement for a transmitter to be present in a low concentration overall, although locally concentrated in specific terminals, also had to be discarded. This necessitated the additional concept of specific metabolic pools with different functions being located in different cells or within different regions of the same cell. Some localization of glutamate and aspartate remote from excitable membranes is clearly essential since their overall brain concentrations would be sufficient to maximally depolarize the majority of neurones in the brain. The concept of separate metabolic pools has been supported by studies on turnover rate. see Chapter 5

Oxidants, Antioxidants And Free Radicals Steven Baskin, Harry Salem, 2017-11-01 This volume collates articles investigating antioxidant, oxidant and free radical research. It examines the role of such research in health and disease, particularly with respect to developing greater understanding about the many interactions between oxidants and antioxidants and how such substances may act as natural protectants and/or natural toxicants.

Parkinson's Disease and Related Disorders, 1973

Clinical Applications of Biomolecules in Disease Diagnosis Ram Lakhan Singh, Pankaj Singh, Neelam Pathak, 2024-10-15 This textbook introduces the clinical applications of biomolecules in disease diagnosis, covering a range of topics in biochemistry. The book discusses carbohydrate and protein metabolism abnormalities, lipid digestion and absorption defects, disorders of purine and pyrimidine metabolism, and the chemistry and biological roles of water and fat-soluble vitamins. It also covers the roles of different macroelements and essential trace elements in physiological processes and the prevention of chronic diseases. The final chapter focuses on recent developments in our understanding of the role of enzymes in disease development and diagnosis. The book chapter also explores the causes and effects of free radicals in the body, including oxidative stress and diseases such as cardiovascular and neurodegenerative diseases. Finally, the chapter discusses cancer development, causes, diagnosis methods, biomarkers, and current treatments such as targeted drug therapy, chemotherapy, and radiation therapy. This book is a useful resource for undergraduate and postgraduate students, researchers, and practitioners in biochemistry, medicine, and health sciences.

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