

Preface

With the recently perceived increase in incidence of autism and the realization that “autism” may actually be “autisms” with subsets of affected individuals, researchers have been pursuing the possibility that there may be multiple etiologies for the disorder. Although most autism studies have focused on genetics and advanced neuroimaging, there is a paucity of research aimed at determining the neurochemical basis of autism. Identifying core neural substrates or key biomarkers is essential to understanding the mechanistic basis that may in part underlie “autisms.” Alterations in molecules, proteins, receptors, and synaptic elements are some of the contributing substrates that could result in altered developmental processes, changed synaptic function, and aberrations in connectivity. It is now apparent that multiple brain areas are affected in autism, and neuropathological defects have been described within cortical and subcortical networks. Although recent progress has been made in identifying some of the genes that may underlie the disorder, much attention has also been given to epigenetic and/or environmental factors that may contribute to subsets of autistic individuals.

The contributors to this book were hand selected because of their expertise in their respective fields. Individually each chapter presents a unique perspective into the clinical, developmental, neurochemical, and/or physical chemical basis of autism. The contributing authors summarize current research findings in their respective areas and also present novel ideas and propose hypotheses and possible mechanisms that may be operative during development and the potential consequences of having defects in specific molecules, receptors, or genes.

The subtitle “From Molecules to Minicolumns” was inserted because of much recent attention given to alterations in the basic organization of mini- or micro-columns of neurons in cerebral cortical areas in autism. These especially include prefrontal cortical areas that undergo an overgrowth during early postnatal development in many individuals with autism. To this end, the world renowned Dr. Alan Peters, the neuroanatomist that originally described mini- or micro-columnar organization in the cerebral cortex, was recruited to write a chapter in this book giving his expert perspective on the issue in autism.

The book begins with highly respected clinician, Dr. Margaret L. Bauman, Director of the LADDERS clinic in the Boston area, with a clinical and medical perspective of autism discussing etiologies, clinical presentation, early identification,

advancements in medical care, and associated disorders. In the chapter “The Male Prevalence in Autism Spectrum Disorders: Hypotheses on its Neurobiological Basis”, Italian researchers Drs. Flavio Keller and Liliana Ruta present neurochemical hypotheses as the basis for the predominance of male prevalence in autism discussing the possible roles of estrogen, testosterone, oxytocin, and vasopressin in the organization of brain circuits and hemispheric specialization. Psychiatrist Dr. Ricardo Vella relates neuropathologies in autism, in the limbic and cerebellar regions, to specific behaviors and presents a developmental perspective and hypotheses regarding emotional and attachment behaviors in autistic individuals. The chapter “The Morphology of Minicolumns” continues on the neuropathology theme by the aforementioned Dr. Alan Peters, an intensive review on normal minicolumn organization and how it is altered in normal aging, Alzheimer’s disease and autism. This is essential reading to understand the basic structural and functional unit of cortical organization and how it is affected in neurobiological disease states.

The chapter “The Developmental Neuropathology of Autism” contributed by the well-recognized neuropathologist, Dr. Thomas Kemper, relates neuropathological changes in autism to the pre- and postnatal developmental timing of the disorder. Defects in cellular pathology such as abnormal cell size, ectopic neurons, decreased numbers of neurons, and/or possible myelination defects are related to abnormal patterns of brain growth and developmental timing in autism. Neurochemical defects during development is the theme of the next chapter contributed by Dr. Diane Chugani discussing using positron emission tomography (PET) molecular imaging providing information regarding time course differences in the ontogeny of various neurochemical processes in children with autism. Dr. Chugani describes how developmental changes in serotonin synthesis and GABA_A receptor binding in children are important in developing new therapies during critical developmental windows.

The chapter “Glutamic Acid Decarboxylase (GAD) as a Biomarker of GABAergic Activity in Autism: Impact on Cerebellar Circuitry and Function”, contributed by the Editor and colleagues, focuses on changes in the cerebellum in autism and how alterations in mRNA in key synthesizing enzymes for GABA (GAD65 and GAD67) underlie defective circuitry with potential consequences for output projections to thalamic, cortical, and/or subcortical regions and the effect on motor and/or cognitively based behaviors. With all the recent attention on chromosomal defects in autism such as duplications/deletions in chromosome 15q11–13 region that contains three GABA_A receptor subunit genes, Dr. Amber Hogart and renowned researcher Dr. Janine LaSalle present the chapter “Epigenetic dysregulation of 15q11-13 GABA_A Receptor Genes in Autism” on epigenetic dysregulation of gene effects on this region in autism and in a variety of neurodevelopmental disorders. Drs. Mukaetova-Ladinska, Westwood, and Perry and in chapter “Cholinergic Component of Autism Spectrum Disorder” describe changes in muscarinic and nicotinic cholinergic receptor changes in autism brain areas in children and adults. The authors also discuss the use of cholinesterase inhibitors and receptor antagonists as intervention therapies for treatment of cognitive and non-cognitive behavior changes in autism spectrum disorders (ASDs). The chapter “Oxytocin and Autism” revisits the role of oxytocin in autism focusing on its role in social behavior.

Drs. Peter Kirsch and Andreas Meyer-Lindenberg from Mannheim, Germany, are experts on the prosocial neuropeptide oxytocin and discuss its role in humans and its relevance for autism pathogenesis and therapy. In the chapter “The Role of the Noradrenergic System in Autism Spectrum Disorders”, Dr. David Beversdorf presents the normal role of norepinephrine and its effects on cognition and the possible dysregulation of norepinephrine in autism and possible treatment with propranolol.

Dr. Richard Deth and colleagues in the chapter “Oxidative Stress in Autism and Its Implications for Dopamine-Stimulated Phospholipid Methylation” discuss the relationship of oxidative stress and autism. Impaired methylation is a consequence of oxidative stress, and the authors present a discussion of how metabolic events contribute to impaired methylation and the role of dopamine D4 receptor activation in gamma frequency synchronization of neural networks during attention which is thought to be defective in autistic children. At the synaptic level, Drs. Craig Powell and Antony Boucard discuss the important topic of mutational defects in specific types of postsynaptic neuroligin-3 and -4 linked to the presynaptic cell adhesion molecule neurexin-1 affecting trans-synaptic bridges in rare cases of autism in the chapter “Neuroligins and Neurexins: Synaptic Bridges Implicated in Autism”. The authors describe in detail the mechanisms that underlie such defects and present an animal model and its effectiveness. Perhaps the most innovative chapter is the one presented by Dr. Peter Bergathon, a neurologist, physicist, and physical chemist who is an expert in neuroscience systems “intelligence modeling” and applies its principles to develop a novel hypothesis based on the energy demands of certain types of computational strategies in the brains of individuals with autism. The energetics of information transfer in the autistic knowledge surfaces for solving system analysis problems including language and reciprocity are unfavorable compared to manifolds associated with more natural behaviors. Some may find this fascinating treatise challenging, but Dr. Bergathon’s analysis suggests that autistic behaviors may be the result of an attempt to manage a highly unfavorable energy cost when cognitive dynamical processes are demanded from a neural system ill suited for these tasks.

In the final chapter, an expert pharmacologist, Dr. Terrell Gibbs presents a comprehensive review of pharmacotherapies in autism. He details their results from clinical trials, their effectiveness, and their role in the treatment of autistic behaviors. Special emphasis is given to the atypical antipsychotic drug risperidone that is frequently effective for ameliorating symptoms of irritability, hyperactivity, social withdrawal, and stereotypic, repetitive behavior in autism.

In summary, this book presents a fresh perspective on some of the groundbreaking research and novel hypotheses being applied to the neurochemical, developmental, and physiochemical etiologies and treatments of autism. Included is an Appendix with lay summaries of all chapters in the book to help the educated lay individual in understanding these presentations by experts in the field. The book is aimed at contributing to the understanding of autism as well as advancing our knowledge in developing effective pharmacotherapies. The hope is that with continued efforts and contributions from the scientific community, individuals with autism

will find effective and treatment improvements in their lives. The authors and editor would like to thank the families for their unending campaign to support research efforts and raise awareness as well as their generous donations of brain tissue for post-mortem studies.

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