The Neurochemical Basis of Autism
Gene J. Blatt
Editor

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From Molecules to Minicolumns

Springer
To my wife Faith and my family for their love and support and to families of individuals with autism for their strength, perseverance, and unwavering desire to find answers.
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-Lindenbergh 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 propanolol.

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 ground-breaking 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.

Boston, MA, USA

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Autism Spectrum Disorders: Clinical and Medical Perspectives

Margaret L. Bauman

Introduction

Autism is a behaviorally defined disorder, first described by Kanner in 1943. The following year, Hans Asperger published a report of four children with “autistic psychopathy” (Asperger, 1944). Since that time, the definition of autism has evolved from the very narrow view of “early infantile autism” to an expanded and more detailed description as delineated in the Diagnostic and Statistical Manual (DSM-IV) (1994). The current classification includes autism within the broader category of pervasive developmental disorder (PDD) along with Asperger’s syndrome, Rett’s Syndrome, childhood disintegrative disorder and pervasive developmental disorder not otherwise specified (PDD-NOS). However, as more clinical investigations and basic science research have become increasingly available over the past several years, it has become apparent that autism involves a continuum of severity and symptoms, and as a result, the term “autism spectrum disorders” (ASD) has come into common usage.

Etiology

Autism is now considered one of the most common disorders of development worldwide. Studies performed by the United States Centers for Disease Control (CDC) in selected communities in 2002 suggest that the current prevalence rates for ASD are approximately 1 in 150 children (Kuehn, 2007). The increase in the reported prevalence of ASD has been attributed by some to improved ascertainment, a broadening of the diagnostic definition, and improved public and professional
awareness. Others have attributed this upsurge in diagnosis to the contribution of potential, as yet to be identified, environmental factors.

Numerous epidemiologic studies have provided compelling evidence for a genetic basis for autism (Bailey et al., 1995; Bolton et al., 1994). Beginning with the seminal twin study of Folstein and Rutter, published in 1977, the concept of ASD as a largely genetic disorder has remained in the forefront of autism research. In this study, the authors identified a higher concordance in monozygotic twins than in dizygotic twins. Since that time, numerous linkage studies have been reported with the most frequently replicated findings being associated with chromosomes 7q, 15q, 22q, and 2q (Schaefer and Mendelsohn, 2008). Additional candidate genes of promise include GABA (gamma amino butyric acid), serotonin transporter genes, Engrailed 2, Neuroligin, MECP2, WNT2, PTEN, and MET (Campbell et al., 2007). Autism is four times more common in males than in females, with a higher ratio in milder forms of the disorder. Further, ASD is associated with a significant familial recurrence, much higher than that seen in the general population. The reported recurrence risk has been estimated to be approximately 15% in families having one affected child (Landa, 2008; Landa and Garrett-Mayer, 2006; Lauritsen et al., 2005). If the family has two affected children, the recurrence rate for subsequent children increases substantially, up to 25–50% (Cook, 2001; Spence, 2004).

Despite modern technology and advanced research, only approximately 6–15% of individuals with autism will be found to have an identifiable genetic diagnosis. In addition, a number of syndromes have been associated with ASD including Fragile X syndrome, Tuberous Sclerosis, Smith–Lemli–Opitz syndrome and Rett syndrome (MECP2 mutations) (Schaefer et al., 2008). Numerous genes have been investigated as possible candidate genes, but replicated findings are lacking. Current epidemiological studies of ASD strongly suggest multifactorial inheritance, including genetic heterogeneity with multiple major gene effects, possibly contributing environmental effects and physiologically linked processes with multiple genes.

One of the many additional potentially important risk factors for ASD that has gained increased interest is the role of advance parental age. In a recent study, Durkin et al. (2008) noted that in a study of 1251 children with complete parental age information and who were defined as having ASD based on DSM-IV criteria, both maternal and paternal age were independently associated with autism. The authors also noted that firstborn offspring of two older parents were three times more likely to develop autism than were later born offspring. A number of potential mechanisms for these effects have been suggested including age-related chromosomal changes, complications of pregnancy, or possible environmental exposures during pregnancy that could have mutagenic effects. In addition, given the apparent importance of birth order, the authors speculate that these children may be more susceptible to autoimmune responses affecting neurodevelopment or may be affected secondary to maternal exposure to neurotoxic chemicals, passed to the offspring transplacentally or in breast milk, in combination with advanced maternal age. Whatever the mechanisms involved, these observations warrant further investigation in a larger population of ASD children.
Clinical Presentation

Although it is now recognized that autism is a clinically and biologically heterogeneous disorder, those affected share a triad of common features which include atypical social interaction, delayed and disordered language, and a markedly restricted repertoire of activities and interests (American Psychiatric Association, 1994). Symptoms can range from relatively subtle and mild to very severe. For example, there may be a qualitative impairment in reciprocal social interaction as opposed to an absolute absence of social interaction. Social behaviors can range from a seemingly total lack of awareness of others to inappropriate eye contact and atypical social responsiveness. Communication skills can span from a total lack of verbal speech and intentional use of gesture to the presence of speech that is associated with atypical intonation, prosody, syntax, and grammar. Although the normal development of single word receptive and expressive vocabulary may be present, pragmatic language may be significantly impaired. Many affected individuals demonstrate poor eye contact, echolalia, pronoun reversals, stereotypic and repetitive behaviors, sensory processing dysfunction, difficulty dealing with novelty, and an obsessive reliance on routine and some level of cognitive impairment. In very young children, the lack of a pointing response and joint attention and limited pretend play are frequent characteristics as early as 12 months of age. Many affected individuals have exceptional islands of rote memory and outstanding isolated talents in the face of otherwise general functional disabilities. Although it was initially believed that approximately 75% of those affected with autism functioned in the mentally retarded range, more recent studies have found that fewer than half of affected individuals have significant cognitive impairment (Newschaffer et al., 2007).

Typically, those individuals with non-syndromic or “essential” autism demonstrate few if any dysmorphic features and are generally described as very attractive appearing children. For many years, these children were believed to demonstrate no abnormalities of motor function or if present, these deficits were believed to be merely associated symptoms. It has now become apparent that gross and fine motor dysfunction is more common than previously appreciated. Numerous clinical studies indicate that children with autism exhibit deficits in skilled motor performance in response to command and with tool use, suggestive of a more generalized dyspraxia (Rogers et al., 1996; Mostofsky et al., 2006). Children with autism often show delays in learning novel complex motor skills such as peddling a tricycle or pumping on a swing with their legs (Gidley Larson and Mostofsky, 2006). Further, in a study of motor impairment in a group of 154 ASD children, Ming et al. (2007) noted that hypotonia was the most common motor symptom in this cohort, with motor dyspraxia being more prevalent in younger children than older children. Gross motor delay was reported in 9% and toe walking in 19%. The etiology of motor dysfunction in ASD remains uncertain with abnormalities of the cerebellum, basal ganglia, and/or neural connections across distributed networks being hypothesized (Gidley Larson et al., 2008).

The role of the clinician is to try to identify specific etiologic factors that may contribute to the diagnosis of ASD and then to provide appropriate guidance and counseling based on the information obtained. Frequently, the parent is the first
to raise concerns about their child’s development with their medical provider and these concerns need to be taken seriously by the health-care community. Despite significant advances in basic science and clinical research, the diagnosis of ASD remains largely a clinical one, based largely on behavioral history and developmental assessments and observation. Although not typically used on a routine basis by primary care physicians, formalized internationally accepted measures such as the Autism Diagnosis Interview-Revised (ADI-R) and the Autism Diagnostic Observation Schedule-Generic (ADOS-G) are used in many specialty clinics and research programs and have resulted in a greater reliability in diagnosis (Lord et al., 1994, 2000). According to its current definition, the clinical features of autism typically become evident before 3 years of age and are usually associated with varying degrees of developmental delay.

For the average primary care physician, the ADI-R and ADOS-G are too time intensive to administer in a busy pediatric and family medicine practice. However, there are now a number of screening tools and parent questionnaires available that can be used. Although not considered to be adequate to make a definitive diagnosis, these tools can identify potential risk factors and clinical signals that should then lead to a referral for further assessment.

Examination of the autistic child, adolescent, and adult may be complicated by variable levels of cooperation, impaired communication, and behavioral issues. Important factors during the physical and neurological assessments should include identification of potential dysmorphic features that might suggest a specific diagnosis or syndrome. Measurements of head circumference throughout childhood has resulted in the observation that a subset of ASD children demonstrate a larger than average head circumference, with approximately 20% of these showing a frank macrocephaly of greater than 98% for age and sex. More recent work by Lainhart et al. (2006) highlight the fact that the distribution curve of head size in ASD is similar to that seen in typically developing children but is shifted to the left, suggesting that this unusual head growth may reflect an up-regulation of as yet unknown growth factors. The clinical finding of macrocrania is, at this time, without a defined neuropathological correlate.

All patients with autism should have a formal audiogram. Many ASD children present with impaired receptive and expressive language and fail to respond to the spoken word, causing some parents to wonder if their child might be deaf. Impaired hearing could alter communication and socialization skills. There is a debate as to the role of electroencephalography (EEG) as part of the routine evaluation of a child with ASD. Although there are reports of autistic-like symptoms in some children with seizure disorders and an acquired aphasia (Landau–Kleffner Syndrome), this disorder is very rare. In general, EEG is probably not indicated as a routine part of the ASD evaluation unless there is a clinical history to suggest a possible seizure disorder. Similarly, cranial imaging studies are not routinely recommended unless abnormalities on neurological examination are observed (Filipek et al., 1999). Additional assessments should include high resolution karyotype and Fragile X studies as an initial step, along with assessments from a speech and language pathologist, an occupational therapist, and a cognitive developmental specialist.