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The neurochemical underpinnings of autism spectrum disorder

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Abstract

Autism spectrum disorder encompasses a range of neurobehavioral and neurodevelopmental conditions marked by deficits in social interaction and communication, as well as restricted and repetitive behaviors or interests, alongside atypical sensory processing. Environmental, immunological, genetic, and epigenetic factors contribute to the pathophysiology of autism, triggering neuroanatomical and neurochemical changes early in central nervous system development. Numerous neurochemical pathways contribute to the etiology of autism spectrum disorder; however, the interactions among these intricate networks and their role in the emergence of core autism symptoms remain poorly understood. Additional research on neurochemical changes in autism is essential to elucidate the early neurodevelopmental differences that contribute to the significant heterogeneity of autism spectrum disorder, thereby informing new strategies for treatment and prevention.

Keywords: glutamate; gamma-aminobutyric acid; dopamine; serotonin; oxytocin; acetylcholine; N-acetyl aspartate

The neurochemical aspects of autism

Autism spectrum disorder encompasses a range of neurobehavioral and neurodevelopmental conditions marked by deficits in social interaction and communication, as well as restricted and repetitive behaviors or interests, and atypical sensory processing. [1] The prevalence of autism has risen markedly over the past two decades, increasing from two to five per 10,000 children to 1 in 59 children (1 in 37 boys and 1 in 151 girls), with males being four times more likely to be affected than females. [2] Growing evidence highlights the biological foundations of autism. Onset symptoms are typically observed before the age of three, with changes in social behavior or other mild autistic features often noted within the first few months of life. [3] This indicates that neuroanatomical and neurochemical events related to the pathophysiology of autism occur early in the development of the central nervous system. Research indicates that autism frequently coexists with various neurological and psychiatric disorders, including global developmental delay, cognitive deficits, epilepsy, electroencephalographic anomalies, sleep disorders, developmental coordination disorder, neuropathies, Tourette syndrome, anxiety, oppositional defiant disorder, conduct disorder, attention deficit hyperactivity disorder, mood disorders, psychosis, personality disorder, post-traumatic stress disorder, eating disorders, gender dysphoria, and substance abuse. [4] Additionally, various medical conditions are comorbid with autism, including immunological disorders, gastrointestinal diseases, and sleep-related breathing disorders. Several genetic syndromes are also commonly associated with autism, such as fragile X syndrome, Rett syndrome, Angelman syndrome, tuberous sclerosis complex, Phelan-McDermid syndrome, Timothy syndrome, and neurofibromatosis type 1. [5] These factors contribute to phenotypic heterogeneity, which reflects a complex multifactorial etiology of autism spectrum disorder. This has prompted most researchers to adopt a dimensional perspective on autism instead of a categorical approach. The etiopathogenesis of autism spectrum disorder remains largely unknown. This condition is multifactorial, arising from both genetic and environmental influences. Furthermore, evidence indicates that autism possesses a significant genetic component.

The prevalence of autism among siblings of affected individuals ranges from 2.9% to 3.7%, indicating an almost 100-fold increased risk relative to the general population. [6] Twin studies indicate concordance rates ranging from 36% to 91% for monozygotic twins, while dizygotic twins exhibit a concordance rate of 1%. [7] Initial data regarding the role of neurotransmission in autism emerged several decades ago from postmortem brain studies and bodily fluid measurements. More recent advancements include molecular imaging and genetic evidence related to neurotransmitters. Neurotransmitters and neuropeptides are essential for normal brain development and are involved in the regulation of memory, behavior, and motor activity. [8] They influence neuronal cell migration, differentiation, synaptogenesis, apoptosis, and synaptic pruning. A dysfunction in the neurotransmitter system can result in impairments in brain development processes, which may contribute to autism. [9] Autism spectrum disorder constitutes a complex neurobehavioral syndrome, with no specific causes currently identified. Anatomical brain abnormalities, genetic anomalies, and neurochemical dysfunctions involving neurotransmitters and neuropeptides such as gamma aminobutyric acid, glutamate, serotonin, dopamine, N-acetyl aspartate, oxytocin, arginine-vasopressin, melatonin, vitamin D, orexin, opioids, and acetylcholine are implicated in the onset of autism. Numerous pathways contribute to the determination of autism; however, the interactions among these biological systems are not well understood. Additional studies on neurochemical networks related to early neurodevelopmental alterations are necessary. Enhancing the comprehension of the mechanisms underlying the etiology of autism spectrum disorder poses a significant challenge, primarily due to the considerable heterogeneity associated with the condition. There is a presence of multiple dysregulated neurotransmitters and neuropeptides in both animal models and individuals with autism. While evidence indicates that certain receptor anomalies contribute to specific phenotypic variations, it remains challenging to delineate the pathogenetic role of each neuronal receptor in shaping the autism phenotype. This framework provides partial explanations for certain clinical features of autism spectrum disorder, including alterations in sensory integration and neuropsychological and psychological dysfunction. The heterogeneity of autism complicates the identification of exclusive neurobiological and genetic characteristics associated with autism spectrum disorder. Currently, there are only a limited number of replicated neurochemical findings.

Further efforts are necessary to determine if these anomalies play a primary etiological role or if they are secondary epiphenomena resulting from a global cerebral dysfunction. Most research on autism etiology tends to focus on specific behavioral domains or individual impairments rather than the entire autism phenotype. Research advancements may yield novel therapeutic strategies that could enhance and potentially prevent symptoms of autism. We advocate for the conduct of higher quality studies to elucidate which receptor systems may serve as effective pharmacological targets for the treatment of autism symptomatology.

In conclusion, further evidence regarding the neurochemical alterations associated with autism is necessary. Enhanced understanding in this domain may facilitate novel pharmacological management strategies and the identification of biomarkers with improved specificity and sensitivity. Additional research is necessary in this domain to address the deficiencies in the treatment of this disease.

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