Review / Derleme

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Decoding Autism: The Role of Synaptic Dysfunction in Neurodevelopment

Otizmin Şifresini Çözmek: Nörogelişimde Sinaptik Disfonksiyonun Rolü

Filiz Çetinkaya[1,2,3], Duygu Bandırmalı[2,3,4,5], Güvem Gümüş-Akay[1,2,3,4,5]

1 Ankara University, Graduate School of Health Sciences, Department of Interdisciplinary Neuroscience, Ankara, Turkey
2 Ankara University, Brain Research Center (AÜBAUM), Ankara, Turkey
3 Ankara University, Neuroscience and Neurotechnology Center of Excellence (NÖROM), Ankara, Turkey
4 Ankara University, Graduate School of Health Sciences, Department of Physiology, Ankara, Turkey
5 Ankara University, School of Medicine, Department of Physiology, Ankara, Turkey

ABSTRACT

The human brain is comprised of intricate neuronal networks that comprise approximately 100 trillion synapses, which underpin functional connectivity. Disruptions in these synaptic connections play a fundamental role in several neurological disorders, such as autism spectrum disorder (ASD). During early development, genes related to ASD, coupled with environmental stressors, effect brain development and neural circuit formation. Genes associated with the structure and functioning of synapses demonstrate a significant prevalence of mutations within individuals diagnosed with ASD. In addition, environmental factors and mitochondrial dysfunction affecting synaptic metabolism also contribute to the pathophysiology of ASD. Understanding the link between synaptic dysfunction and autism symptoms may provide new perspectives for therapeutic approaches. The purpose of the present analysis is to furnish the reader with an overview of the findings pertaining to synaptic dysfunction in ASD.

Keywords: Autism spectrum disorder, Synaptic transmission, Synapse

ÖZET

İnsan beyni, yaklaşık 100 trilyon sinaps içeren karmaşık nöronal ağlardan oluşmakta ve bu yapılar, işlevsel bağlantısallığın temelini oluşturmaktadır. Bu sinaptik bağlantılardaki bozulmalar, otizm spektrum bozukluğu (OSB) da dahil olmak üzere çeşitli nörolojik hastalıklarda kritik bir rol oynamaktadır. Erken gelişim sürecinde, OSB ile ilişkili genler çevresel stres faktörleri ile birlikte beyin gelişimini ve nöral devre oluşumunu etkilemektedir. Sinaptik yapı ve işlevle ilişkili genler, OSB'de belirgin şekilde mutasyona uğramaktadır. Ayrıca, sinaptik metabolizmayı etkileyen çevresel faktörler ve mitokondriyal işlev bozukluğu da OSB'nin patofizyolojisine katkıda bulunmaktadır. Sinaptik disfonksiyon ile otizm semptomları arasındaki ilişkinin anlaşılması, terapötik yaklaşımlar açısından yeni bakış açıları sunabilir. Bu derleme, OSB'de sinaptik disfonksiyon ile ilgili bulguların genel bir değerlendirmesini sunmayı amaçlamaktadır.

Anahtar Kelimeler: Otizm spektrum bozukluğu, Sinaptik iletim, Sinaps

Introduction

Autism spectrum disorder (ASD) is a complex neurodevelopmental condition that affects early intellectual development. It is characterized by impaired motor coordination, deficits in social communication, and repetitive, restricted behaviors. ASD was originally categorized into multiple diagnoses, including Asperger's disorder, childhood disintegrative disorder, and pervasive developmental disorder-not otherwise specified, but these are now unified under the broader ASD classification (1).

The etiology of ASD involves a heterogeneous mix of genetic and environmental factors. Genome-wide association studies have been undertaken to identify rare variants, single nucleotide polymorphisms (SNPs), and de novo copy number variations (CNVs) contributing to ASD risk. These have led to the discovery of many ASD-associated genes, now included in major genomic databases (2).

Corresponding author: Güvem Gümüş-Akay
Ankara University, School of Medicine, Department of Physiology, Ankara, Turkey
E-mail: guvemakay@gmail.com **ORCID ID:** 0000-0002-6564-3133
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Recent findings suggest these genetic alterations converge on core neurodevelopmental pathways (3). Neurobiological studies show dysregulation in gene expression—via epigenetics and transcription—alongside disrupted synaptic communication and neurotransmission. Many ASD-related genes are expressed during critical stages of brain development, from prenatal to early postnatal periods (4), and their protein products are regulated by neural activity via transcription, splicing, translation, and degradation (5).

At the structural level, synapses represent the fundamental communication units between neurons, composed of a presynaptic terminal that releases neurotransmitters, a synaptic cleft, and a postsynaptic membrane equipped with specialized receptors (6). Genes such as *NRXN, NLGN, SHANK3,* and *DLG4*—frequently implicated in ASD—play essential roles in synapse formation, stabilization, and signal transduction (7). Animal and genetic studies consistently demonstrate that mutations in these and other ASD-related genes, including *FMR1, MECP2, UBE3A,* and *TSC1/2,* lead to disruptions in synaptic integrity and circuit-level connectivity, ultimately contributing to deficits in social interaction, sensory processing, and cognitive function (8-11). Together, these findings highlight synaptic dysfunction as a central mechanism in ASD pathophysiology (12).

The following sections examine core molecular mechanisms underlying synaptic dysfunction in ASD, with a particular focus on synaptic cell adhesion molecules, postsynaptic scaffold and signaling proteins, mitochondrial impairment, and the resulting excitation/inhibition (E/I) imbalance. While additional contributors—such as epigenetic modulation, impaired synaptic pruning, and environmental factors—are also implicated in ASD pathophysiology, they are only briefly addressed or remain beyond the scope of this review.

Synaptic Cell Adhesion Molecules

Synaptic cell adhesion molecules (CAMs) play a central role in establishing and maintaining synaptic connectivity. By spanning the synaptic cleft, these molecules mediate structural alignment between pre- and postsynaptic neurons and modulate key processes such as synaptogenesis, synaptic stabilization, and plasticity mechanisms including long-term potentiation (LTP) and long-term depression (LTD) (13). Among the CAMs, neurexins (NRXNs), neuroligins (NLGNs), and Contactin-Associated Protein-Like 2 (CASPR2) have been extensively linked to ASD through both genetic and functional studies.

Neurexins

NRXNs are presynaptic adhesion molecules that interact with postsynaptic neuroligins (NLGNs) to form trans-synaptic complexes essential for synaptic differentiation and communication. The three NRXN genes—*NRXN1, NRXN2,* and *NRXN3*—each produce multiple alpha and beta isoforms that regulate synapse specificity, plasticity, and neurotransmitter release (14).

Disruptions in NRXNs, particularly *NRXN1*, are among the most frequently reported mutations in ASD. Both gene deletions and duplications impair synaptic transmission, disturb E/I balance, and lead to altered neural circuitry associated with social deficits and repetitive behaviors (15).

Studies on *Nrxn1* knockout (KO) mice show impairments in synaptic organization and cognitive functions, underscoring its role in neurodevelopment (16). Given their central function in synaptic communication, *NRXNs* remain a major focus in ASD research, particularly with regard to understanding how their dysfunction impacts neural circuit formation and cognitive processes (17). The investigation of these molecules may offer valuable insights that could inform the development of therapeutic strategies aimed at restoring synaptic balance in individuals with ASD.

Neuroligins

NLGNs are postsynaptic adhesion molecules that play a crucial role in synapse identity and functional development (14). They interact with presynaptic NRXNs to facilitate synapse formation and stabilization. NLGNs exist in multiple isoforms, each with distinct localization and functional properties. Specifically, NLGN1 is primarily found in glutamatergic excitatory synapses, while NLGN2 is localized to γ-aminobutyric acid-ergic (GABAergic) inhibitory synapses, playing a crucial role in maintaining E/I balance (18).

Functional studies demonstrate that *NLGN1* overexpression increases excitatory signaling and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) to NMDA (N-methyl-D-aspartate) receptor ratios, while *NLGN2* overexpression strengthens inhibitory responses (19, 20). Notably, *Nlgn1* KO mice exhibit impaired hippocampal LTP, reduced dendritic spine density, and increased repetitive grooming behavior—core features of ASD. The phenotypes observed in these models, including spatial memory deficits and disrupted corticostriatal signaling, support a critical role for NLGNs in synapse morphology and ASD-like behavior (19).

Contactin-Associated Protein-Like 2

CASPR2, encoded by the *CNTNAP2* gene, is a member of the NRXN family. CASPR2 was initially identified as a synaptic protein involved in synapse formation and maintenance, but recent research has expanded its functional relevance to neurodevelopmental processes. CASPR2 plays significant roles in dendritic arborization, dendritic spine stabilization, and AMPAR trafficking, highlighting its importance in neuronal connectivity and signaling (21, 22).

The presence of recessive mutations and chromosomal inversions in the *CNTNAP2* gene has been identified in individuals diagnosed with both intellectual disabilities and ASD. *CNTNAP2,* alongside genes such as *KMT2C* and *SHANK3,* has been associated with ASD, speech, and language impairments. These mutations are known to disrupt critical protein domains involved in language-related neural functions (23, 24).

Cntnap2 KO mice exhibit ASD-like behaviors including repetitive actions, restricted social interactions, and impaired communication (21). These models also show disrupted cortical inhibitory interneuron migration, further supporting *CNTNAP2*'s contribution to the neural mechanisms underlying ASD (22). Additionally, CNTNAP2 dysfunction is associated with altered sensory processing, likely due to impaired Kv1 potassium channel function, which contributes to neuronal hyperexcitability and pain hypersensitivity (25).

SNP rs2710102 in the *CNTNAP2* gene has been associated with language development deficits in ASD. Individuals carrying the A-allele tend to exhibit lower language skills compared to G-allele homozygotes, despite no significant difference in overall communication abilities. Moreover, studies in *Cntnap2*-deficient mice showed that dysfunction of this gene influences affective processing beyond basic sensory and motor domains (26). These findings highlight the gene's broad involvement in both synaptic and circuit-level phenotypes relevant to ASD.

Postsynaptic Density and Scaffold Proteins

The postsynaptic density (PSD) is a protein-dense region located at the postsynaptic membrane of excitatory synapses, essential for regulating synaptic transmission and plasticity (6). This specialized structure hosts neurotransmitter receptors, kinases, structural proteins, and signaling molecules essential for synaptic function (27).

Scaffold proteins, as core components of the postsynaptic density (PSD), organize and stabilize multiprotein complexes at synaptic sites. Through interaction domains such as PDZ (PSD-95/Discs large/ZO-1) and SH3 (Src Homology 3), they orchestrate intracellular signaling cascades and modulate synaptic structure in an activity-dependent manner (28). Disruptions in these proteins lead to synaptic instability and are linked to ASD-related neurodevelopmental deficits (29).

PSD-95

PSD-95, encoded by *DLG4,* is a key scaffold protein at glutamatergic synapses, regulating receptor clustering, dendritic spine morphology, and NMDA receptor-mediated plasticity (27). It plays a central role in trafficking NMDA and AMPA receptors and in maintaining synaptic integrity during maturation (30).

Mutations in *DLG4* have been associated with increased ASD risk, and loss-of-function variants impair synaptic connectivity, leading to social and cognitive dysfunctions (27, 31). Proteomic analyses in individuals with idiopathic ASD indicate downregulation of PSD-95-associated complexes, contrib-

uting to delayed synaptic maturation and cognitive impairment (32).

Animal models revealed that environmental exposures can alter PSD-95 expression, disrupting plasticity and inducing ASD-like behaviors (33). *Dlg4* KO mice exhibit repetitive behaviors and social deficits, while pharmacological upregulation of PSD-95 restores synaptic function and ameliorates behavioral abnormalities in ASD models (34).

HOMER Protein Family

The HOMER family consists of three homologous genes—*HOMER1, HOMER2,* and *HOMER3*—encoding proteins that act as multimodal scaffolds. These proteins interact with type I metabotropic glutamate receptors (mGluR1–5), SH3 and multiple ankyrin repeat domains (SHANK) proteins, and inositol1,4,5-trisphosphate receptors (IP3Rs), anchoring them to cytoskeletal components and supporting synaptic signaling and plasticity. HOMER proteins are essential for cell signaling, neuronal excitability, synaptic neurotransmission, and neural plasticity (35).

Two experimental findings link HOMER dysfunction to ASD: First, *Homer1a* is upregulated in the basolateral amygdala (BLA) of valproic acid (VPA)-exposed rats, a widely used ASD model. Overexpression of *Homer1a* in the BLA of healthy mice induces ASD-like behaviors, such as impaired fear conditioning and reduced social interaction (36). Second, HOMER1A a interacts with SHANK3, and disruption of this interaction affects synaptic plasticity and connectivity, suggesting a mechanistic pathway contributing to ASD phenotypes (37).

SH3 and multiple ankyrin repeat domains protein 3

SHANK3 is a key postsynaptic scaffold protein highly enriched in the postsynaptic density (PSD) of excitatory synapses. It plays a central role in synaptic organization by linking neurotransmitter receptors, such as NMDA and AMPA receptors, to intracellular signaling complexes and the actin cytoskeleton. SHANK3 directly interacts with PSD-95, HOMER, and other Membrane-Associated Guanylate Kinase (MAGUK) proteins, thereby contributing to synaptic strength, plasticity, and spine morphology (28).

Genetic studies have identified *SHANK3* mutations and deletions as one of the most consistent and penetrant monogenic causes of ASD (38). Animal models with *Shank3* deficiency exhibit core ASD-like phenotypes, including impaired social behaviors, repetitive actions, and disrupted synaptic transmission (39). Given its structural and functional significance, SHANK3 represents a critical node in the molecular architecture of ASD-related synaptic dysfunction.

The Discs Large Protein Subfamily

DLG proteins, including DLG1, DLG2, DLG3, and DLG4, are members of the MAGUK family and regulate glutamatergic receptor positioning and postsynaptic signaling. These proteins contain three PDZ domains and serve as scaffolds for NMDA and AMPA receptor complexes, and link extracellular stimuli to postsynaptic signaling pathways (40, 41).

In addition to postsynaptic roles, DLG proteins influence ion channel trafficking, presynaptic excitability, and neurotransmitter release (42). Their differential expression across development suggests stage-specific functions (30). Genetic variants in the *DLG1* gene and 3q29 microdeletions have been associated with ASD and schizophrenia (43). In mice, *Dlg2* (PSD-93) deficiency results in reduced corticostriatal synaptic transmission and ASD-like behaviors, including social withdrawal and cognitive inflexibility (44).

Figure 1 highlights the NRXN–NLGN trans-synaptic complex, postsynaptic scaffold proteins (PSD-95, SHANK, HOMER), and their roles in anchoring AMPA and NMDA receptors at excitatory synapses.

Synaptic Signaling and Protein Synthesis Regulators

Synaptic signaling and protein synthesis are critical for neurodevelopment and cognitive function. In ASD, disruptions in these processes contribute to abnormal plasticity, impaired neuronal communication, and altered protein regulation. Key molecular regulators of these pathways include Fragile X Mental Retardation Protein (FMRP), Tuberous Sclerosis Complex (TSC), Phosphatase and Tensin Homolog

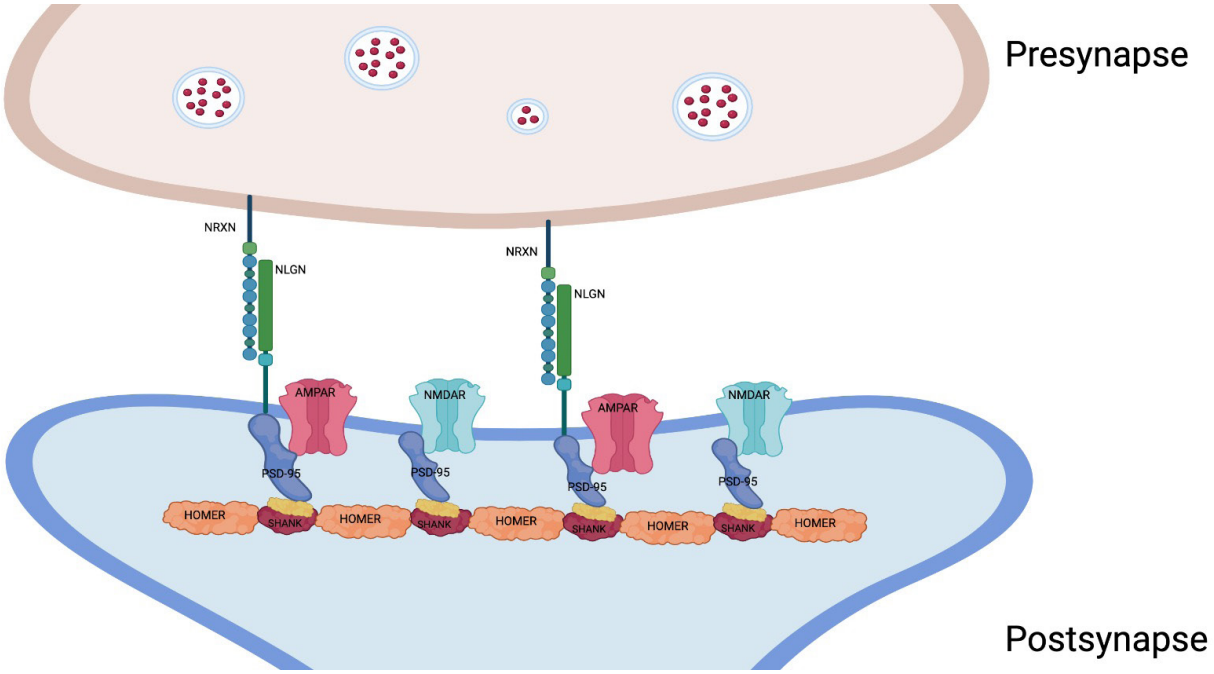


Figure 1. NRXN–NLGN trans-synaptic complex, postsynaptic scaffold proteins (PSD-95, SHANK, HOMER), and their roles in anchoring AMPA and NMDA receptors at excitatory synapses.NLGN: neuroligins, NRXN: Neurexins, PSD95: Post-synaptic Density Protein 95, SHANK: SH3 and multiple ankyrin repeat domains protein. This figure was created using a personally licensed BioRender account.

(PTEN), Methyl-CpG Binding Protein 2 (MECP2), and Ubiquitin-Protein Ligase E3A (UBE3A). Mutations or dysregulation of these proteins are strongly implicated in ASD pathophysiology and represent promising targets for therapeutic intervention (45).

Fragile X Mental Retardation Protein

FMRP is an RNA-binding protein encoded by the *FMR1* gene and is essential for local protein synthesis at synapses. Its loss leads to Fragile X Syndrome (FXS), the most common inherited cause of intellectual disability and a well-established monogenic contributor to ASD. Approximately 20–30% of males with FXS meet full ASD diagnostic criteria, and 2–4% of ASD cases are linked to FXS (46). FXS is caused by CGG trinucleotide repeat expansion (>200 repeats) in the promoter region of *FMR1,* leading to transcriptional silencing. In addition, point mutations have been observed to contribute to FXS pathogenesis, albeit less frequently.

FMRP regulates synaptic plasticity by controlling the translation of specific mRNAs, including those related to dendritic spine maturation. *Fmr1* KO models exhibit social deficits, seizures, anxiety, and synaptic abnormalities—features overlapping with ASD (47). While the exact mechanism linking FXS and ASD remains unclear, studies using human genetics and animal models suggest that FMRP interacts with key translation regulators such as CYFIP1 and eIF4E. Dysregulation of these interactions alters protein synthesis and contributes to ASD-related phenotypes (45, 48)

TSC1/TSC2 complex

The *TSC1* and *TSC2* genes encode hamartin and tuberin, which form a complex that negatively regulates the mammalian target of rapamycin (mTOR) pathway, a central mediator of cell growth and metabolism. Mutations in either gene cause TSC, a multisystem disorder often presenting with epilepsy, intellectual disability, and ASD. Up to 36% of individuals with TSC mutations develop ASD features (21).

Loss of TSC function results in hyperactive mTOR signaling, disrupting synaptic plasticity and neuronal morphology (49). Impaired synaptic plasticity, neuronal morphological abnormalities, and aberrant cell growth and proliferation are observed in TSC-related conditions (50). *TSC2* mutations are particularly enriched among individuals with ASD, further implicating the mTOR pathway in ASD pathophysiology (49).

Phosphatase and Tensin Homolog

PTEN is a tumor suppressor gene that antagonizes the PI3K/AKT/mTOR pathway. While best known for its role in cancer, germline *PTEN* mutations are also associated with neurodevelopmental abnormalities and ASD (51).

Approximately 10-20% of individuals with ASD and macrocephaly harbor PTEN mutations (52). These mutations have also been observed in Cowden syndrome, a condition characterized by macrocephaly and increased cancer risk. Some individuals with Cowden syndrome have been found to exhibit autistic traits (53). Genetic sequencing of the PTEN gene in ASD patients has identified three heterozygous germline mutations and one missense mutation (54).

Mouse models with *Pten* mutations (e.g. *Pten*$^{m3m4/m3m4}$) display ASD-like behaviors and molecular hallmarks of ASD (55). Studies have shown that ASD- and cancer-associated *PTEN* germline mutations predominantly occur in the ATP-binding motif type B and around the highly conserved P-loop in the active site, supporting their pathogenic significance (56). Furthermore, PTEN regulates alternative splicing of ASD-associated transcripts, affecting synaptic function and gene expression regulatory processes. This mis-splicing is developmentally regulated and involves other susceptibility genes, underscoring the multifactorial nature of PTEN-associated ASD (52).

Methyl-CpG Binding Protein 2

MECP2 encodes a transcriptional regulator that plays a crucial role in neuronal development, and its mutations are known to cause Rett Syndrome (RTT) and ASD (57). Loss of *MECP2* function leads to delayed language development, psychomotor regression, seizures, and impaired social interactions following an initial period of normal development (58). Studies suggest that MECP2 deficiency is linked to Brain-Derived Neurotrophic Factor (BDNF) dysregulation, cytokine production in astrocytes, and impaired neuronal dendritic branching (59). Additionally, MECP2-deficient astrocytes fail to support normal dendritic morphology in wild-type neurons (60). In *Mecp2*-null mice, astrocyte-specific restoration of *MECP2* expression was found to rescue normal neuronal dendritic morphology, improving locomotion, anxiety, and respiratory deficits (61). *MECP2* mutations and duplications have been identified in ASD cohorts and are linked to stereotypic behaviors, communication deficits, and sensory abnormalities (62, 63).

Ubiquitin-Protein Ligase E3A

UBE3A is a dual-function protein that acts as both a ubiquitin ligase and a transcriptional co-activator. Loss of maternal *UBE3A* expression leads to Angelman Syndrome (AS), characterized by severe intellectual disability, ataxia, epilepsy, and autistic features (64, 65).

Some experts classify AS as a syndromic form of ASD, as studies indicate that a subset of AS individuals meet the full diagnostic criteria for ASD (66). In ASD individuals, 15q11-q13 duplications are among the most common chromosomal abnormalities (67). This region includes the PWS/AS critical locus, which is subject to genomic imprinting. While maternally inherited duplications in this region are strongly associated with ASD, paternally inherited duplications tend to result in a normal phenotype (68). These findings underscore the critical role of UBE3A and 15q11-q13 genomic variations in ASD, highlighting their impact on neurodevelopment and potential therapeutic targets for intervention (69).

Synaptic Metabolic Stress and Excitatory/Inhibitory Imbalance in ASD

Emerging evidence suggests that disruptions in neuronal metabolism and synaptic energy homeostasis are closely linked to E/I imbalance, a core feature in the pathophysiology of ASD. Synaptic transmission is highly energy-dependent, requiring tightly regulated ATP production, calcium buffering, and redox homeostasis to maintain functional neurotransmitter signaling. Mitochondrial dysfunction, frequently reported in ASD, impairs these processes and disrupts the delicate balance between excitatory glutamatergic and inhibitory GABAergic signaling (70, 71).

Mitochondrial Dysfunction and Synaptic Vulnerability

Mitochondria are essential for sustaining synaptic plasticity and neuronal survival through ATP synthe-

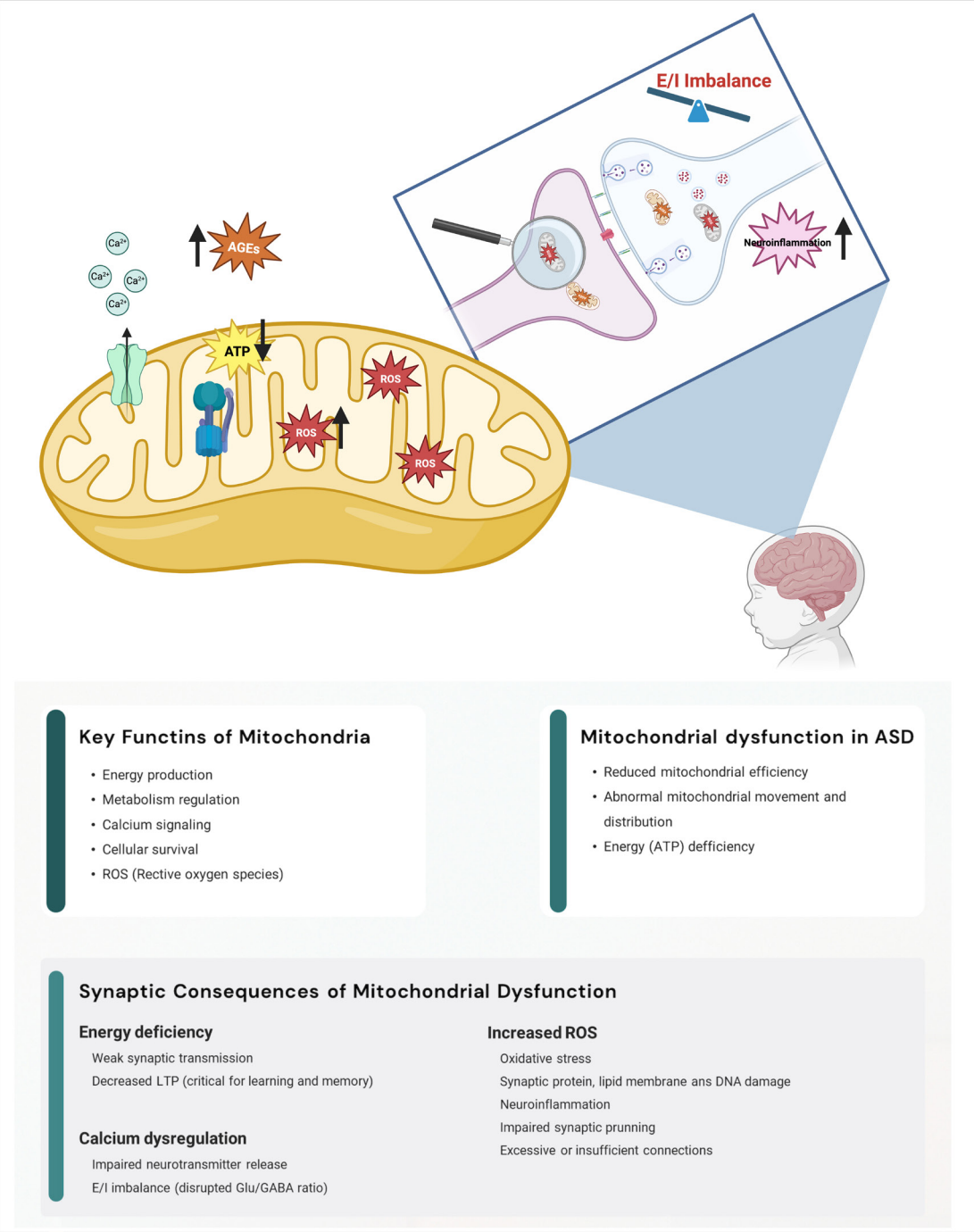


Figure 2. The schematic illustration of mitochondrial dysfunction in ASD. Arrows pointing upwards represent increases, whereas arrows pointing downwards represent decreases. AGEs: advanced glycation end-products, ROS: reactive oxygen species. This figure was created using a personally licensed BioRender account.

sis, calcium regulation, and reactive oxygen species (ROS) detoxification. Studies have shown that neurons from individuals with ASD exhibit impaired mitochondrial movement, abnormal distribution at synaptic terminals, and reduced respiratory efficiency (72). Such dysfunction compromises LTP-related processes and synaptic pruning, both vital for cognitive development and circuit refinement.

Elevated ROS levels can damage synaptic lipids and proteins, disrupt calcium-dependent vesicle release, and promote neuroinflammation. Postmortem studies confirm elevated oxidative stress in ASD brains, implicating mitochondrial redox imbalance in synaptic pathology (73). Furthermore, in syndromic ASD models such as FXS, mitochondrial impairment is closely linked to FMRP deficiency, affecting both energy metabolism and synaptic transmission (45, 73).

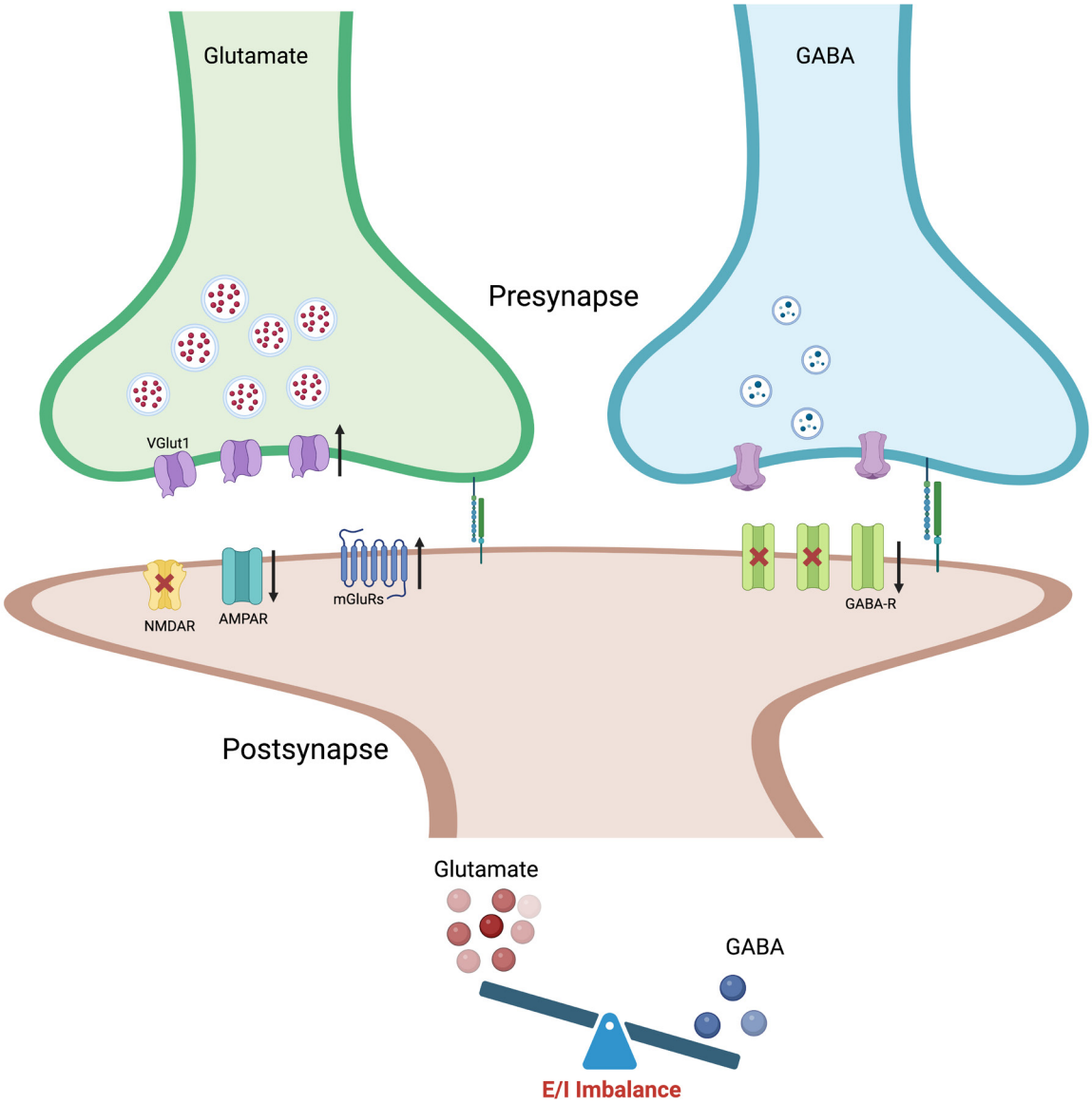


Figure 3. The schematic illustration of excitatory/inhibitory imbalance in ASD. Arrows pointing upwards represent increases, whereas arrows pointing downwards represent decreases. A cross (X) symbol denotes dysfunction in the corresponding component. AMPAR: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors, GABA: Gamma-aminobutyric acid, NMDAR: N-methyl-D-aspartate receptors, VGlut1: Vesicular glutamate transporter 1, mGluRs: metabotropic glutamate receptor. This figure was created using a personally licensed BioRender account.

Recent pharmacological studies targeting synaptic mitochondria have shown promise. For instance, activation of 5-HT1A receptors via eltoprazine improved mitochondrial performance and synaptic function in a Drosophila FXS model (74). Additionally, the accumulation of advanced glycation end-products (AGEs) and their precursor methylglyoxal (MG) has been linked to mitochondrial dysfunction and synaptic impairments, contributing to cognitive decline. Samantha et al. (2025) have examined the role of AGE and MG accumulation in synaptic mitochondrial stress and transmission in transgenic mice. The study found that overexpression of glyoxalase 1 (GLO1), an enzyme that detoxifies AGEs, reduced AGE accumulation, restored mitochondrial function, and improved cognitive performance in aging mice. Ex vivo and in vitro studies on hippocampal neurons confirmed that GLO1 rescued LTP and synaptic transmission, mitigating synaptic plasticity deficits (75).

Frye et al. (2024) further demonstrated that individuals with ASD and neurodevelopmental regression (NDR) exhibit hyperactive yet fragile mito-

chondrial respiration, showing reduced resilience to oxidative stress compared to typically developing siblings (76). Taken together, these findings underscore the vulnerability of synaptic mitochondria in ASD. Importantly, mitochondrial impairments not only disrupt local synaptic energy metabolism and calcium signaling but also converge on one of the core neurobiological mechanisms of ASD: E/I imbalance. Figure 2 illustrates the key functions of mitochondria at the synapse and the consequences of mitochondrial dysfunction, including ATP deficiency, oxidative stress, impaired calcium buffering, and downstream effects on E/I balance.

Excitation/Inhibition Imbalance and Synaptic Signaling Disruption

The fine-tuned balance between excitatory glutamatergic and inhibitory GABAergic neurotransmission is crucial for normal brain development, synaptic plasticity, and cognitive function. Disruption of this E/I balance represents a core pathophysiological mechanism in ASD, contributing to altered network dynamics and behavioral abnormalities (77). Figure 3 visually summarizes key alterations in excitatory and inhibitory synaptic components—including changes in receptor expression and presynaptic transporters—culminating in the disrupted E/I balance observed in ASD.

GABAergic Dysfunction in ASD

GABA is the major inhibitory neurotransmitter in the brain. Dysfunction of GABAergic signaling has been extensively documented in ASD. Ionotropic *GABAA* and metabotropic *GABAB* receptor genes—particularly *GABRB3* and *GABRA5*—are located within the 15q11–q13 chromosomal region, which is frequently duplicated in individuals with ASD (78, 79).

Mouse models of this duplication recapitulate ASD-like behaviors, including poor social interaction, behavioral inflexibility, and abnormal ultrasonic vocalizations (80). Postmortem studies have revealed reduced expression of GABAergic genes and related proteins in ASD brain tissue (81). Furthermore, the expression of GABAB receptors, particularly GABAB1 and GABAB2, has been found to be decreased in ASD brain samples, which may be critical for maintaining the E/I balance (82).

Glutamatergic Signaling Alterations

Glutamate serves as the primary excitatory neurotransmitter in the central nervous system. Its receptors include ionotropic types (AMPA, NMDA, and kainate receptors) and metabotropic types (mGluRs) (83). The paucity of postmortem tissue available for research has restricted the progress of studies on glutamate receptor expression in ASD. Nevertheless, postmortem cerebellar tissue samples have revealed a reduction in AMPAR density and an increase in mGluRs expression, suggesting altered glutamatergic signaling in ASD (84). Changes in AMPAR subunit expression influence LTP and LTD, fundamental mechanisms linked to learning and memory. Disruptions in these mechanisms could contribute to cognitive deficits in ASD (47).

NMDAR dysfunction has been observed in *Shank3, Nlgn1, Fmr1* KO mice, and *Mecp2* transgenic mouse models (85). Although *Nlgn1*-KO mice display increased repetitive behaviors, they do not exhibit the full spectrum of autism-associated behavioral impairments. Mutations in the genes encoding glutamate receptors, particularly *GRIN2B, GRIN2A,* and *GRIK2* have been associated with ASD in human genetic studies (86).

Among metabotropic receptors, mGluR1 and mGluR5 have been the most extensively studied in ASD and related disorders, including FXS, obsessive-compulsive disorder, and intellectual disability (87). Elevated mGluR5 protein levels have been reported in the vermis region of the cerebellum in children with ASD compared to controls (88). *mGluR5* KO mice exhibit cognitive deficits, highlighting its importance in synaptic regulation (89).

Epigenetic and Structural Contributors to E/I Imbalance

Emerging evidence suggests that E/I imbalance in ASD may also result from transcriptional and epigenetic dysregulation. Histone modifications such as H3K4me2/3, H3K9ac, H3K27ac, H3K9me2, and H3K27me3 have been shown to affect the expression of the genes related to excitatory and inhibitory

transmission in the prefrontal cortex of ASD patients (90). Additionally, synaptic structural studies using VGlut1 (presynaptic excitatory marker) and PSD-95 (postsynaptic marker) revealed increased excitatory and decreased inhibitory synapse numbers in the upper cortical layers of ASD brains, confirming functional synaptic imbalance (91). Conditional KO mice for *Arid1b*, an ASD risk gene, also demonstrate interneuron dysfunction and cortical hyperexcitability, further supporting the genetic basis of E/I dysregulation (92).

Environmental Influences on Synaptic Function

Beyond genetic and cellular mechanisms, growing evidence highlights the significant impact of environmental factors on synaptic dysfunction in ASD. Microglial cells, which support synaptic homeostasis and pruning, have been implicated in ASD pathophysiology. Dysfunction in these cells may lead to neuroinflammation and impaired synaptic refinement, both of which can disrupt neural circuit development (93).

Environmental insults during prenatal development may alter microglial activity, contributing to E/I imbalance and aberrant network formation. For instance, a recent mouse study examined the effects of valproic acid (VPA) and Poly I:C exposure during embryogenesis. Male offspring exhibited both stereotypical behaviors and impaired social interactions, while female mice showed only repetitive behaviors. Remarkably, restoration of GABA levels on postnatal day 10 prevented the onset of ASD-like behaviors, suggesting that environmental factors can perturb neurotransmitter balance and synaptic function (94).

Additionally, prenatal exposure to endocrine-disrupting chemicals such as Bisphenol A (BPA) and its analogs has emerged as a potential risk factor. 4-hydroxyphenyl 4-isoprooxyphenylsulfone (BPSIP), a BPA substitute, is frequently detected in breast milk and placental tissue. A 2024 study by Zhang et al. demonstrated that early-life exposure to BPSIP (0.02–0.5 mg/kg/day) in mice led to increased anxiety and impaired spatial memory in both sexes. Synaptic plasticity was altered via changes in Synapsin I (SYN1) and PSD-95 levels in the cerebellum and hippocampus (33).

It should be noted that these examples represent a subset of known environmental contributors to ASD. Due to space constraints, only select cases are highlighted here.

Therapeutic Approaches and Future Directions

Several studies have focused on targeting synaptic dysfunction in ASD, exploring various synaptic proteins, ion channels, and regulatory mechanisms. These therapeutic approaches can be classified into pharmacological and non-pharmacological interventions (78). Research has demonstrated that impairments in AMPAR-mediated neurotransmission are linked to autism, particularly in conditions involving SHANK3 or SYNGAP1 protein dysfunction. The use of AMPAR modulators, such as Perampanel, has been proposed as a potential treatment for these synaptic dysfunctions (95).

Another promising avenue is the development of genetic-based interventions, including Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-based gene editing, which aims to correct mutations affecting synaptic function. Such approaches are currently under investigation for their potential in restoring normal synaptic signaling in ASD (96, 97).

Conclusion

Taken together, these findings suggest that synaptic dysfunction in ASD arises from complex interactions among adhesion molecules, postsynaptic scaffold proteins, intracellular signaling pathways, mitochondrial impairments, and neurotransmitter imbalance. Figure 4 provides an integrative schematic representation of the excitatory and inhibitory synapses, highlighting how synaptic, signaling, and metabolic components converge to drive ASD-related neurodevelopmental disturbances. Therapeutic efforts focusing on restoring synaptic function through targeted pharmacological treatments and genetic interventions hold promise for future treatment strategies. Continued research is necessary to further elucidate the molecular underpinnings of ASD and develop effective, personalized therapies to improve outcomes for individuals affected by the disorder.

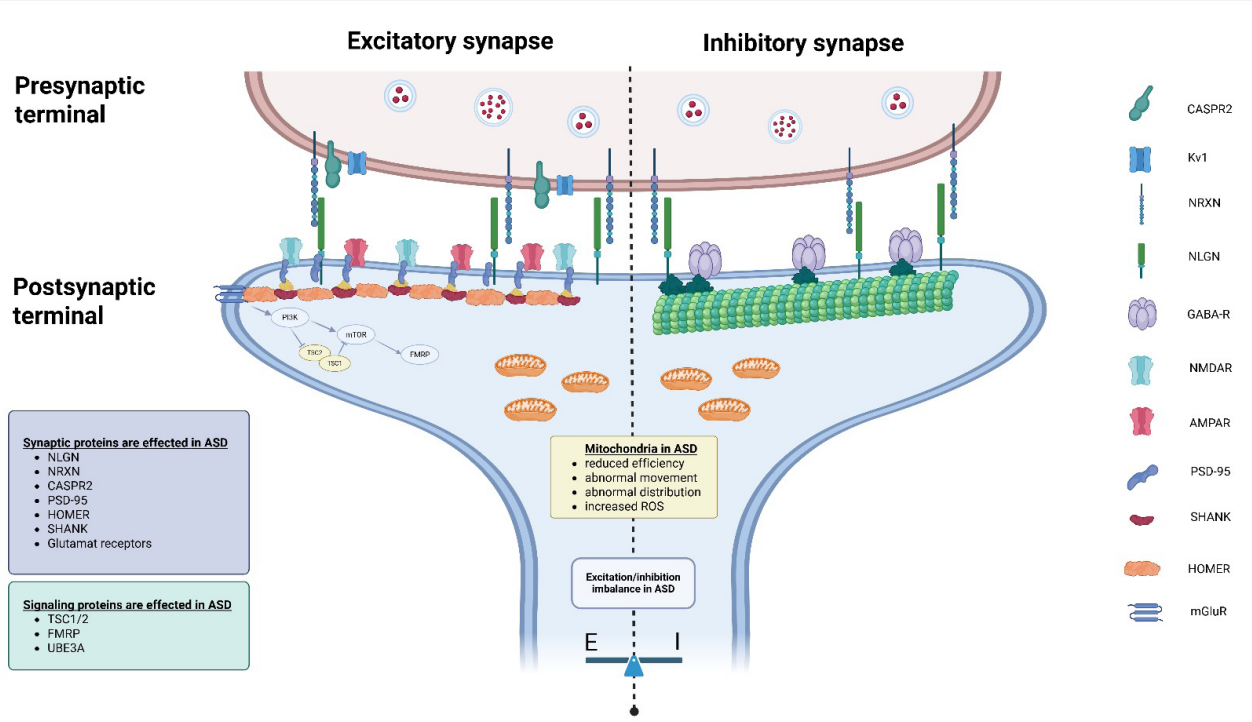


Figure 4. The schematic representation of the key synaptic and signalling proteins affected in autism spectrum disorder (ASD). The excitatory synapse illustrates the involvement of postsynaptic glutamate receptors (AMPA, NMDA, mGluR), scaffold proteins (PSD-95, SHANK, HOMER), and the neurexin–neuroligin adhesion complex, while the inhibitory synapse displays GABA receptors and associated presynaptic elements. The inclusion of proteins such as TSC1/2, mTOR, FMRP, and UBE3A is intended to represent altered intracellular signalling pathways. Mitochondria have been observed to reflect ASD-related changes, including reduced efficiency, abnormal distribution, and increased ROS. The imbalance between excitation and inhibition (E/I) is central to the pathophysiology of ASD, resulting from both synaptic structural and functional alterations. GABAR: Gamma-aminobutyric acid receptor. This figure was created using a personally licensed BioRender account.

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