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Autism and Epilepsy: Synaptic Dysfunction Plays a Role in Both Entities

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Author's contribution

The sole author designed, analyzed, interpreted and prepared the manuscript.

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ABSTRACT

Autism is associated with synaptic dysfunctions, leading to disturbances in neural circuit connectivity. The result is an impaired synaptic pruning process, which removes extra connections, causing an overabundance of the synaptic system in autistic brains. Mutations in genes associated with synapse formation, elimination, transmission, and plasticity also contribute to this dysfunction, potentially changing social communication and behavior. During brain development, healthy brains undergo synaptic pruning, where unnecessary connections are eliminated. Especially in autism spectrum disorders, this process is often less effective, leading to a change of number of synapses. This higher number of synapses can disrupt normal communication pathways, contributing to autistic symptoms. Different genes associated with an increased risk for autism also play important roles in synaptic maturation and function. Mutations in these genes can lead to defects in synapse

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formation, maintenance, and communication. Many different proteins are essential for synapse function, such as those encoded by genes like SHANK3, are often affected in autism spectrum disorders. Defects in these proteins can alter synaptic structure and signaling, impacting synaptic plasticity. The combination of increased synapse numbers and impaired synaptic function can result in disturbed neural circuit connectivity. This disrupted connectivity affects how the brain processes information and relates to the core symptoms of autism, including difficulties with social communication and repetitive behavioral symptoms. Synaptic dysfunction plays an important role in the co-occurrence of autism spectrum disorders and epilepsy forms, as it underlies the common neurobiological features shared by both conditions. Disrupted synaptic function, which involves the communication between neurons, leads to an imbalance between excitatory and inhibitory signals in the brain, increasing the risk for both ASD-related challenges and epileptic seizures. This dysfunction can stem from genetic mutations affecting synaptic proteins or other cellular processes, leading to both developmental delays, autism-like behaviors, and increased susceptibility to seizures. Further research has to focus on the biochemical mechanism of synaptic function and dysfunction in both entities in childhood.

Keywords: Autism-child; synapse; dysfunction; epilepsy; mutation.

1. INTRODUCTION

Understanding synaptic dysfunction as a key mechanism in autism suggests that interventions targeting synaptic processes could be a promising therapeutic strategy. Studies in animal models with autism-related genetic mutations have shown that correcting abnormal synaptic pruning or function can improve autistic-like behaviors, indicating that these phenotypes might not be entirely irreversible. Shared pathophysiology and a core mechanism in both ASD and epilepsy is the abnormality in how neurons communicate through synapses, the junctions where signals are transmitted. Synaptic dysfunction can disrupt the balance between excitatory (activating) and inhibitory (calming) neurons, a fundamental aspect of brain function that is often disturbed in both ASD and epilepsy. Other shared pathways include abnormalities in cell signaling and cell proliferation, which are crucial for brain development and can be affected by genetic factors. Many genetic mutations and syndromes that cause ASD also increase the risk of epilepsy, leading to the term "syndromic autism". These genetic variants can directly impact synaptic proteins and neuronal circuits, causing both conditions. The brain's ability to adapt and change its synaptic connections (synaptic plasticity) is particularly active during early development. Disruptions during this vulnerable period can lead to long-lasting effects, contributing to both autistic traits and epilepsy. Abnormalities in processes like synaptic pruning—the elimination of faulty neuronal connections—can result in "over-connectivity" or altered communication between brain regions, a feature seen in both autism and epilepsy. Well-known genetic conditions like Fragile X syndrome and Tuberous Sclerosis Complex are examples where single gene disorders can cause both autistic phenotypes and epilepsy. Pathogenic variants in the DNM1 gene can lead to severe neurodevelopmental issues, including epilepsy and autistic traits. Research using human cerebral organoids shows that microglial cells, when exposed to SCN2A mutations associated with ASD, can increase the elimination of postsynaptic components, affecting synaptic function.

1.1 Synaptic Adhesion Molecules (SAM) and their Impact on Synapse Formation

Neurexin and Neuroligin are the SAMs with the greatest influence on synaptic formation, with other important molecules being EphB/Ephrin-B, immunoglobulin (Ig)-containing SAMs, Cadherins, and SynCAMs. These molecules facilitate synaptogenesis by connecting pre- and postsynaptic terminals and organizing the components within them, with specific subtypes determining whether they are involved in excitatory or inhibitory synapses. Restoring Munc-13-1 mitigates presynaptic pathology. Neurexin and Neuroligin are a central pair of SAMs, with Neurexin being presynaptic and Neuroligin postsynaptic, forming a transsynaptic complex crucial for the formation of both excitatory and inhibitory synapses. EphB and Ephrin-B are a pair of SAMs that control synaptic development by regulating the localization and function of glutamate receptors. Immunoglobulin (Ig)-containing SAMs are a family of molecules, including SynCAMs, that play a role in synapse

formation and modulation of synaptic plasticity, influencing activity-dependent remodeling of synapses. Like Neurexin and Neuroligin, Cadherins contribute to both the general formation of synaptic contacts and the determination of specific synaptic partners. As members of the Ig domain SAM family, SynCAMs contribute to synaptic plasticity by shaping synapses and promoting activity-dependent remodeling. SAMs act as "bridges" connecting pre- and postsynaptic neurons and providing the basis for stable synaptic connections.

1.2 Synaptic Dysfunction as a Key Feature of Autism

Synaptic dysfunction is a key feature of Autism spectrum diseases, most often from genetic mutations affecting synaptic proteins or environmental factors that disrupt correct brain development (Xian et al., 2025). Research reflects disturbances in synaptic pruning, synapse numbers, and function in individuals with autism disorders, possibly contributing to the condition's characteristic social and behavioral challenges. Targeting synaptic pathways, neuroinflammation, and synaptic excitability may offer therapeutic strategies for ASD. Abnormal synaptic pruning is one key element during development, the brain refines its neural connections through a process called synaptic pruning. Dysregulation of this process, particularly involving the brain's microglia, has been linked to ASD. Many genes associated with ASD are involved in the structure and function of synapses. These include genes that encode scaffolding proteins and molecules crucial for synapse formation, elimination, and plasticity. Studies using PET scans have shown that autistic adults have fewer synapses than neurotypical individuals. Disrupted synaptic function can lead to altered neuronal signaling, potentially affecting brain network connectivity and contributing to functional under- and overconnectivity observed in the autistic brain (Libera et al., 2025). Mutations in genes like SHANK3 are associated with synaptic dysfunction and are implicated in ASD. Variants in these genes, which encode cell adhesion molecules essential for synapse formation, are also linked to ASD pathogenesis. Microglia brain cells play a role in synaptic pruning. Impaired microglial function, as seen with TMEM59 deficiency, can lead to excessive accumulation of synapses and contribute to ASD-like behaviors. Targeting the inflammatory response in microglia could help improve synaptic pruning and alleviate symptoms. Modulating synaptic excitability and pruning-related molecular pathways offers potential strategies for treating ASD. Further research into the genetic factors that cause synaptic pathology may lead to more targeted interventions (Carter, 2019).

1.3 Specific Genes Associated with Autism (ASD)

Autism Spectrum Disorder (ASD) is associated with rare mutations in over 100 genes, with SHANK3 (Shi et al., 2025, Francavilla et al., 2025, Bae et al., 2025), ADNP (Gualtieri et al., 2025, Kang et al., 2025, Trudler et al., 2025), CHD8, and DYRK1A being frequently identified, often impacting brain development by affecting processes like synaptogenesis (Elkhateeb et al., 2023). These mutations can be inherited or occur de novo, spontaneously in the embryo, and can be found in specific networks of genes that control neuronal development, contributing to a higher likelihood of developing ASD. Researchers have identified numerous genes, including: SHANK3 (Shi et al., 2025, Francavilla et al., 2025, Bae et al., 2025), plays a role in forming neuronal connections; ADNP, involved in brain development; CHD8, a gene where mutations are linked to autism and sometimes other developmental issues; DYRK1A, associated with autism and affects brain development; ARID1B, ASH1L, CHD2, other genes where rare mutations are linked to ASD. CNTNAP2, NRXN1, NLGN4X, MDGA1, DSCAM and Scn2a are genes within the synaptic network that are commonly involved in ASD (Gao et al., 2025, Shih et al., 2025, Karmon et al., 2022). Moreover, mi RNA`s and dysregulation of neuropilin-2-expression seem to play an important role in autism pathogenesis (Kim et al., 2025, Liu et al., 2025, Dhaliwal et al., 2024, Shiu et al., 2025, Ogwo et al., 2025, Altaf et al., 2025, Vidyadhara et al., 2024, Lim et al., 2021, Cheng et al., 2018, Graber et al., 2017). mTORC 1 and 2 seem to play a key role in neural abnormalities of PTEN-deficient human neurons and cortical organoids (Subramanian et al., 2025). Intraneuronal accumulation of amyloid-beta-peptides seems to link to co-morbities of autism (Santhakumar et al., 2024, Sibih et al., 2025).

1.4 Synaptic Dysfunction as a Key Feature of Epilepsy

Synaptic dysfunction is a key feature of epilepsy, involving disruptions in neurotransmitter release,

reception, and synaptic strength, often stemming from genetic mutations affecting proteins in the synaptic vesicle cycle or ion channels. These synaptic abnormalities lead to neuronal hyperexcitability, causing synchronized electrical activity and seizures. Specific molecular dysfunctions, like impairments in vesicle recycling or faulty ion channels, can result in diverse forms of epilepsy, including severe neurodevelopmental disorders. Genetic defects in proteins involved in the synaptic vesicle cycle (e.g., SYN1, STXBP1, DNM1) can hinder the proper release of neurotransmitters, which are essential chemical messengers for neuronal communication. Dysfunctions in long-term potentiation (LTP) and other forms of synaptic plasticity can disrupt the fine-tuning of synaptic connections, contributing to hyperexcitable circuits. Mutations in ion channels (e.g., SCN1A, KCNQ2), which control neuronal excitability and firing patterns, can lead to excessive neuronal activity and trigger seizures. Genes like SYN1 (vesicle pool regulation), STXBP1 (vesicle docking and priming), and DNM1 (vesicle recycling) are involved in the multi-step process of synaptic vesicle release. Changes in postsynaptic receptors, which receive neurotransmitters from presynaptic neurons, can disrupt normal signaling. Mutations in genes for sodium (e.g., SCN1A), potassium (e.g., KCNQ2), and calcium channels have been linked to epilepsy. The core mechanism of epilepsy is characterized by uncontrolled electrical activity in the brain. The disruption of proper neuronal communication and circuit function increases the likelihood of synchronized neuronal discharges, characteristic of epileptic events. The role of synaptic plasticity in the development and progression of epilepsy is a major area of study, with a focus on identifying potential therapeutic targets. Understanding the specific presynaptic and postsynaptic alterations offers potential avenues for developing novel treatments for epilepsy. Argininosuccinic aciduria could play an important role in epilepsia (Frackowiak and Mazur-Kolecka, 2023).

1.5 Specific Genes associated with Epilepsy

Specific genes associated with epilepsy include SCN1A, KCNQ2, and KCNQ3, which code for ion channels critical for neuronal excitability. Other examples are CDKL5 (infantile spasms), ARX and LGI1 (focal epilepsies), and STXBP1 (epileptic encephalopathy). Many identified genes are involved in neuronal function and development, and a wide range of genes, such as ALDH7A1 and PNPO, have been linked to epilepsy and may be targets for gene-directed therapies. SCN1A, SCN2A are genes that code for sodium channels, which are essential for nerve impulse transmission. Mutations are associated with various forms of epilepsy. KCNQ2 and KCNQ3 are involved in potassium channels, and their mutations are linked to epilepsy. GABRA1 and GABRG2 gene mutations, which code for GABA receptors, can lead to epilepsy. Mutations in genes CHRNA4, CHRNB2 coding for nicotinic acetylcholine receptors, are associated with autosomal dominant nocturnal frontal lobe epilepsy (Cortès-Saladelafont et al., 2018, Asch et al., 2025).

2. DICUSSIONS

Shared synaptic patterns in autism and epilepsy include an imbalance between excitatory and inhibitory (E/I) neural activity, synaptic dysfunction involving impaired receptor function and signaling molecules, and abnormalities in synaptic plasticity and synaptogenesis, with a common genetic basis for many individuals with both conditions (Shi et al., 2025, Francavilla et al., 2025) These synaptic disruptions can lead to hyperexcitability and synchronized neuronal discharges, characteristic of epileptic events, and contribute to the atypical connectivity and communication observed in autism spectrum disorder (ASD)(Shi et al., 2025, Xian et al., 2025, Bae et al., 2025, Kim et al., 2025, Subramanian et al., 2025, Elkhateeb et al., 2023). A key commonality is an imbalance in E/I neurotransmission, where there is an overactivity of excitatory signals and/or reduced inhibitory signals, leading to increased overall neuronal excitability. This imbalance contributes to increased short-term plasticity, enhanced synchrony of neural activity, and potentially over-connectivity, which is seen in both epilepsy and autism (Gualtieri et al., 2025, Bae et al., 2025, Liu et al., 2025). Both autism and epilepsy can involve alterations in synaptic plasticity, the brain's ability to change connections. Dysfunction in molecules that regulate synaptic function, including neurotrophins, signaling pathways, and receptors, contributes to these synaptic alterations. Some genetic conditions linked to both disorders result in impaired synaptic function, such as reduced synaptic vesicle fusion, which dysregulates neuronal circuits (Shi et al., 2025, Kang et al., 2025, Francavilla et al., 2025). Disruptions during neurodevelopment can affect normal synaptic development, leading to

atypical patterns of over-connectivity in certain brain regions in individuals with autism, while also predisposing them to epilepsy. In some cases, there is evidence of altered dendritic spine density and cortical over-connectivity that disrupts efficient communication between brain regions (Chen et al., 2025, Moradi et al., 2025, Dimitrov et al., 2025). Many genes implicated in autism and epilepsy affect common biological pathways critical for brain development and function, including gene transcription, cell proliferation, and synaptic growth. A significant overlap exists in the genetic basis of both disorders, with some individuals having genetic developmental and epileptic encephalopathies that manifest with both ASD and epilepsy (Klaustermeier et al., 2025, Chen et al., 2025). Further research should further evaluate the synaptic processes in both entities to rule out, if autism and epilepsy have a significant correlation on synapse function and synapse molecular pathologies (Lee et al., 2016, Witt et al., 2025).

3. CONCLUSION

Further extensive biochemical research must focus on the role of synaptic dysfunctions in autism spectrum disorder and epilepsy in childhood. There is a lack of information concerning the role of different proteins of the SNARE-complex and also the group of synaptic adhesion molecules (SAM) and their impact on synapse formation and synapse function. Recently, new proteiens playing a role in this synaptic system were found and to date, not closer analysed. Research must focus on this topic to understand the relation of autism and epilepsy, possibly to realize autism as a “mild form” of epilepsy.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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