The Role of Synaptic Cargo Transporters in Regulating Neuronal Excitation/Inhibition Balance in Autism Spectrum Disorders: A focus onSyntabulin-Syntaxin 1 A/B Axis

Abstract:
Various cargo vesicles containing presynaptic proteins are transported from the neuronal cell body to the neuronal terminal to aid in active zone formation. Researchers showed altered levels up to 25 different synaptic proteins (SNAP47, GRIA3/4, GAP43, synaptotagmin 2, LRFN2, SV2C) and syntabulin. Syntabulin is a key component gene of a kinesin motor-adaptor complex essential for the forward movement of active zone components in axons. It plays a crucial role in the assembly of presynaptic structures during neuronal development in response to activity. However, the specific membranous cargoes and motor-cargo interactions are not fully understood. Recent research identified a syntaxin-1-binding protein called syntabulin. Syntabulin links syntaxin-containing vesicles to microtubules and moves with syntaxin in neuronal brain processes. Knocking down syntabulin expression or disrupting the syntabulin-syntaxin interaction hinders the attachment of syntaxin-cargo vesicles to microtubules and reduces syntaxin-1 distribution in neuronal processes. Conventional kinesin I heavy chain binds to syntabulin and associates with syntabulin-linked syntaxin vesicles in vivo. Syntabulincould act as a linker molecule that connects syntaxin-cargo vesicles to kinesin I, facilitating the transport of syntaxin-1 to neuronal processes.Syntabulin also regulates neuronal excitatory and inhibitory imbalance by transporting syntaxin 1 B, more than syntaxin 1A, to the presynaptic membrane. The gene for Syntabulinis found on human chromosome 8q23.2, in mouse on chromosome 15. This review shed light on the role of syntabulin-syntaxin 1A/B axisand mention different synaptic cargo transporters which could play any role in autism spectrum disorders. Further research should focus to study synaptopathies in autism spectrum disorders to open new arenas for pharmaceutical interventions.

Keywords:
Autism-Synaptopathy-Synaptobulin-Syntaxin-Kinesin-Cargo-Children

Introduction:

Autism is a complex developmental disorder that affects the central nervous system, leading to disturbances in relationships and communication with other people (1-42). The manifestation is in early childhood and disturbs various functions such as cognition, language, motor skills, emotions, and social interactions. Patients with autism often exhibit behavioral disturbances that can be challenging for caregivers (2,12,24). Children may have difficulty understanding gestures, smiles, or words, struggle to form relationships, and engage in repetitive irritating behaviors (1-42).Children with autism may have restricted interests and activities, exhibit self-stimulating behaviors, and face challenges with eating and sleeping. They may also display specific preferences or routines that can be distressing for caregivers. While some individuals with autism have intellectual disabilities, others may have normal intelligence or excel in specific areas like mathematics or music. The prevalence of autism is estimated to be 5-15 individuals per 10,000 in Germany, with boys being more affected than girls. Despite extensive research, the exact causes of autism remain unclear, and there is currently no cure for the disorder (1-42). However, targeted support and therapy can help improve symptoms and enhance the quality of life for individuals with autism and their caregivers. Recent findings suggests that autism may be linked to synaptopathy, where there is an imbalance between excitatory and inhibitory synapses, though the exact mechanisms are still not fully understood (1,29). Autism presents a range of challenges for individuals and their families, but with personalized interventions and support, significant improvements can be achieved in managing the symptoms and enhancing overall well-being.The formation and maintenance of synapses depend on the transport of synaptic proteins from the cell body to synapses. Disrupted transport may be associated with neurodevelopmental disorders such as autism. Syntabulin serves as a motor adapter for kinesin-1 and synaptic cargos. Defects in syntabulin-mediated transport can lead to decreased synapse formation and maturation, contributing to autism-like synaptic dysfunction and social behavioral abnormalities. Syntabulin expressionpeaks during early postnatal development and decreases with brain maturation. Neurons lacking syntabulin exhibit impaired transport, reduced synapse density, altered synaptic transmission, and behavioral abnormalities resembling autism traits. A human missense variant of syntabulin identified in an autism patient is unable to rescue synaptic deficits in mice lacking syntabulin. Proper distribution of mitochondria in neurons is crucial for neurotransmission, synaptic plasticity, and axonal outgrowth. However, the mechanisms governing mitochondrial trafficking in neurons have been unclear. Former studies reveal that syntabulin plays a key role in this process (1,29). Syntabulin is a peripheral membrane protein that binds to mitochondria through its carboxyl-terminal tail (1,29). Live imaging of cultured neurons shows that syntabulincolocalizes and moves with mitochondria along neuronal processes. Knocking down syntabulin or disrupting its interaction with kinesin-1 impairs the anterograde movement of mitochondria, leading to reduced mitochondrial density in axons. These current findings suggest that syntabulin links mitochondria to the motor protein kinesin-1, facilitating their transport in neurons. Recent studies suggest that disrupted transport mechanisms play a role in synaptic dysfunction and behavioralabnormalities in autism. The role of syntabulin cargo transport in autism is not clearly evaluated and needs further extensive research efforts (1,29).

Synaptogenesis

Synaptogenesis is the process of forming synapses between neurons in the nervous system, particularly active during early brain development. It is vital for neural growth and synaptic pruning. The neuromuscular junction (NMJ) is a well-studied synapse involving a motor neuron, myofiber, and Schwann cell. The motor neuron releases acetylcholine to stimulate muscle contraction. Astrocytes contribute to synapse plasticity. During development, myoblasts, motoneurons, and Schwann cells originate from distinct embryonic regions. Axons are guided by growth cones to connect with myotubes. NMJ synapse development follows specific patterning with midpoints being innervated. Post-synaptic differentiation

involves increased AChR concentration through clustering and gene regulation. Pre-synaptic differentiation includes changes in synaptic volume and vesicle clustering. Synaptic maturation includes synapse elimination, reducing multiple inputs to one. Synapse formation specificity distinguishes between fast and slow-twitch muscle fibers. In the CNS, synaptogenesis shares similarities with the NMJ but involves different neurotransmitters and receptors. Factors regulating CNS synaptogenesis include signaling molecules, morphology, and environmental enrichment. The Wnt protein family contributes to synapse formation in both the CNS and NMJ. In the CNS, Wnts induce presynaptic and postsynaptic terminal formation in various neuronal cell types. In the NMJ, Wnts play a role in AChR clustering and growth cone enlargement. Wnt expression is crucial for synaptic development and plasticity in both systems.
After contact with the motoneuron, the myotube increases AChR concentration at the synapse, improving signal transmission. This is achieved by clustering AChR, up-regulating AChR gene transcription in post-synaptic nuclei, and down-regulating in non-synaptic nuclei. Post-synaptic differentiation may be triggered by neurotransmitters or changes in the extracellular matrix.AChRmultimerization in the post-synaptic membrane is facilitated by Agrin, released by the motoneuron axon. Agrin binds to the MuSK receptor, activating Rapsyn, which promotes AChR clustering in the membrane.Axonal signals regulate gene expression in myonuclei beneath the synapse, leading to localized up-regulation of AChR gene transcription. CGRP and neuregulin released by the axon activate kinases that enhance AChR gene transcription.Activity-dependent repression of AChR gene in non-synaptic nuclei occurs due to the electrical signal generated by the synapse. This ensures AChR localization to the synapse, enhancing signal fidelity.Changes in the developing axon terminal include increased synaptic volume, vesicle clustering, and membrane polarization. Neurotrophins and cell adhesion molecules released from muscle cells mediate these changes.
Synapses segregate as they mature, with all axonal inputs except one retracting. The post-synaptic end plate deepens and forms folds to increase neurotransmitter reception. Schwann cells transition from loose covers to myelinated caps over the neuromuscular junction. Synaptic pruning involves competition between axons, with stronger synapses maintained through synaptotrophins and weaker ones eliminated. Synaptotoxins released from depolarized post-synaptic membranes deter weaker axons. Motoneurons distinguish between fast and slow-twitch muscle fibers through selective or non-selective pathways. Axons recognize fiber types or are guided by predetermined paths to innervate specific muscle fibers. Similarities exist between NMJ and CNS synapses in structure and function. Both exhibit pre- and post-synaptic membrane differentiation, receptor clustering, and synapse elimination. However, CNS synapses involve different neurotransmitters and receptors, and exhibit greater complexity due to multiple inputs and neuronal plasticity.

Neurochemical Aspects of the most important synaptic cargo transporters:

Syntabulin
Syntabulin interacts with PICK1 and ASICs, controlling ASIC protein levels in neurons and contributing to ASIC-mediated acidotoxicity. Synapse formation and maintenance depend on the transport of synaptic proteins from the cell body to distant synapses. Syntabulin acts as a molecular motor adapter and microtubule-associated protein. It is expressed in the hippocampus and in the nervous system. It binds to kinesin family member 5 B (KIF 5 B). Moreover, it plays an important role of transporting active zone components in microtubules to presynaptic membrane, stabilize presynaptic functions and ameliorates synaptic transmission. Syntabulin regulates neural excitability and control presynaptic function. Syntabulin also regulates neuronal excitatory and inhibitory imbalance by transporting syntaxin 1 B, more than syntaxin 1A, to the presynaptic membrane (1). Disrupted transport may be associated with neurodevelopmental disorders such as autism. Syntabulin serves as a motor adapter for kinesin-1 and synaptic cargos. Malfunctions in syntabulin-mediated transport result in decreased synapse formation and maturation, leading to autism-like synaptic dysfunction and social behavioral abnormalities (29). Syntabulin expressionpeaks during early postnatal development and decreases with brain maturation (29). Neurons lacking syntabulin exhibit impaired transport, reduced synapse density, altered synaptic transmission, and behavioral abnormalities resembling autism traits (29). This study highlights the role of impaired transport mechanisms in contributing to synaptic dysfunction and behavioralabnormalities in autism (29).

Synaptosome-associated protein 47 (SNAP47):
SNAP47, also known as Synaptosome-associated protein 47 kDal, is a human protein encoded by the SNAP47 gene (27,28,30). It is associated with various diseases such as non-small cell lung cancer and schizophrenia. SNAP47 belongs to the SNAP protein family, which are t-SNARE proteins involved in vesicle fusion through the formation of the SNARE complex (27,28,30). The gene for SNAP47 is located on chromosome 1 at 1q42.13 and consists of 13 exons and 12 introns spanning 52,693 base pairs. The protein has a common isoform of 419 amino acids with a molecular weight of 47167 M. SNAP47 is a synaptosome-associated protein that plays a role in vesicle fusion processes. SNAP47's secondary structure includes long alpha helices, beta sheets, and random coils, with alpha helices located around amino acids 120-150 and 350-415. The protein is believed to form a compact four-helix complex with membranes. The tertiary structure of SNAP47 has been predicted using I-TASSER, aligning it with other proteins like Yeast V-ATPase and Ufd2 complexed with ubiquitin-like domain Rad23 (27,28,30).Syntaxin 16, a Qa-SNARE protein, plays a crucial role in membrane trafficking, especially at the trans-Golgi network (TGN). Recent studies have revealed its involvement in autophagy. Syntaxin 16 has dual functions in autophagy: it helps transport ATG9a-containing vesicles to autophagosomes and contributes to autolysosome formation. The former function involves a potential SNARE complex with VAMP7 and SNAP-47, while the latter involves recruitment by Atg8/LC3/GABARAP proteins to autophagosomes and endo-lysosomes. This recruitment may provide functional redundancy with the canonical autophagosomeQa-SNARE syntaxin 17 (43). These new insights shed light on the role of syntaxin 16 in autophagy and raise questions about its mechanistic implications, especially in autism spectrum disorder (43).

GRIA3/4
The ionotropic glutamate receptor AMPA 3 (also known as GRIA3) is a human protein that belongs to the group of AMPA receptors. Glutamate receptors are predominant excitatory neurotransmitter receptors in the mammalian brain, consisting of heteromeric protein complexes with different subunits, each containing a transmembrane domain (31-33). They form a ligand-gated ion channel. The GRIA 1-4 receptors (also known as GluR1-4) are classified as AMPA receptors due to their activation by the agonist alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate (31-33). GRIA3 is also

expressed on lymphocytes and has been considered a candidate gene for various disorders, including autism, Rett syndrome, Rasmussen encephalitis, bipolar disorder, and the X-linked mental retardation syndrome Smith-Fineman-Myers syndrome (31-33). A family with X-linked recessive inheritance of mental retardation and autism was studied in a recent publication (44). Clinical data and blood samples were collected for genetic analysis. Mutations in genes associated with intellectual impairment were sequenced using an Ion PGM platform and confirmed with PCR-Sanger sequencing. The patient evaluated showed mild abnormal EEG but no abnormalities on brain MRI or CT scans. Autism behavior checklist scores were 73 and 66 at ages 7 and 13. In this patient, a novel hemizygous mutation, c.64C>T (p.L22F), in the GRIA3 gene was identified in the patient, with the mother as a carrier (44). Predictive tools suggested the mutation to be damaging and disease-causing.The novel mutation c.64C>T (p.L22F) in the GRIA3 gene likely contribute to the mental retardation and autism in this family (44). Due to the variability of symptoms and genetic factors in autism, genetic testing is crucial for accurate diagnosis (44).

Growth Associated Protein 43 (GAP43)

Growth Associated Protein 43 (GAP43) is a protein encoded by the GAP43 gene in humans. It is known as a "growth" or "plasticity" protein due to its high expression in neuronal growth cones during development, axonal regeneration, and phosphorylation after long-term potentiation and learning. GAP43 plays a crucial role in axon and presynaptic terminal function. Its absence leads to death shortly after birth due to axon pathfinding defects. Synonyms for GAP43 include protein F1, neuromodulin, neural phosphoprotein B-50, axonal membrane protein GAP-43, calmodulin-binding protein P-57, nerve growth-related peptide GAP43, and neuron growth-associated protein 43. Functionally, GAP43 is a nervous tissue-specific cytoplasmic protein that can be membrane-bound through palmitoylation. It is a major substrate for protein kinase C (PKC) and is essential for neurite formation, regeneration, and plasticity. GAP43 is involved in CNS development beyond axonal effects, as it plays a role in centrosome localization and neurogenic cell divisions. Its phosphorylation by PKC regulates neurite formation, regeneration, and synaptic plasticity. Deletions in the GAP43 gene in humans result in the failure to form telencephalic commissures and intellectual disability.
There is an urgent need for animal models of autism spectrum disorder (ASD) to understand the pathology and develop new treatments. The synaptic growth-associated protein-43 (GAP43) is a candidate gene for autism. Previous studies on GAP43 (+/-) mice have shown brain abnormalities consistent with ASD (34). Researchers hypothesized that these mice would exhibit autistic-like behaviors. GAP43 (+/-) mice showed resistance to change, stress-induced withdrawal, and anxiety, similar to ASD symptoms (43). Both GAP43 (+/-) and wild-type mice displayed low sociability and lack of social novelty preference, resembling ASD traits (34). The strain-specific low sociability may aid in studying GAP43-mediated deficits. Further research on these mice could reveal underlying mechanisms for these behaviors (35).

Synaptotagmins

Synaptotagmins are a group of 17 proteins localized to cell membranes, characterized by an N-terminal transmembrane region (TMR), a variable linker, and two C-terminal C2 domains (C2A and C2B) (36-40). There are several protein groups carrying C2 domains related to synaptotagmins, including Ferlins, E-Syts, MCTPs, as well as RIMs, Munc13s, and B/K. Based on their endocrine distribution in the brain and their biochemical abilities, synaptotagmin C2 domains bind calcium (36-40). Therefore, synaptotagminsare believed to serve as calcium sensors that control the release of neurotransmitters and hormones. Although all synaptotagmins are structurally similar, only eight bind calcium (37). Proteins from the synaptotagmin group are involved in exocytosis in both the early (docking of synaptic vesicles to the presynaptic membrane) and late phases through interactions with β-neurexin and SNAP-25.Synaptotagmin 1 can displace Complexin from the SNARE complex in the presence of calcium, considered one of the final chemical reactions in exocytosis (37). The C2 domains then regulate the fusion of synaptic vesicles during exocytosis.

LRFN2 (Leucine Rich Repeat And Fibronectin Type III Domain Containing 2; syn. Synaptic Adhesion-Like Molecule 1)

LRFN2 is predicted to modulate chemical synaptic transmission and regulate postsynapse organization. LRFN2 is a protein-coding gene located in the plasma membrane, active in the Schaffer collateral - CA1 synapse and cell surface, and an integral component of the postsynaptic density membrane. It is associated with Autism Spectrum Disorder and Epilepsy and is involved in pathways related to transmission across chemical synapses and protein-protein interactions at synapses (41). LRFN2 promotes neurite outgrowth in hippocampal neurons, enhances the cell surface expression of NMDA receptor subunits GRIN1 and GRIN2A, and may play a role in redistributing DLG4 to the cell periphery (41). Lrfn2/SALM1 is a synapse adhesion molecule that interacts with PSD-95 and is linked to learning disabilities in humans. However, its role in higher brain function and the underlying mechanisms are not well understood. In a recent study, researchers found that Lrfn2 knockout mice display autism-like behaviors, such as social withdrawal, reduced vocal communication, increased stereotyped activities, and deficits in prepulse inhibition, along with improved learning and memory (41). In the hippocampus, levels of synaptic PSD-95 and GluA1 were reduced, and synapses showed structural and functional immaturity with spindle-shaped spines, smaller postsynaptic densities, decreased AMPA/NMDA ratio, and enhanced LTP (41). In vitro experiments demonstrate that the interaction between Lrfn2 and PSD-95 is crucial for the synaptic surface expression of AMPAR (41). Additionally, researchers identified functionally defective LRFN2 missense mutations in patients with autism and schizophrenia. These findings suggest that Lrfn2/LRFN2 play a key role in the maturation and maintenance of excitatory synapses, and their dysfunction leads to immature or silent synapses with pathological consequences (41).

SV2C(Synaptic Vesicle Glycoprotein 2C)

SV2C is predicted to enable transmembrane transporter activity and seems to be involved in chemical synaptic transmission, as neurotransmitter transport, and transmembrane transport (42). It is predicted to be located in plasma membrane and synaptic vesicle. It seems to be active in neuron projection and synaptic vesicle membrane. It is predicted to be integral component of synaptic vesicle membrane. SV2C is a protein coding gene. Diseases associated with SV2C include botulism. Among its related pathways are bacterial toxins and infectious diseases. Gene Ontology (GO) annotations related to this gene include *transporter activity* and *transmembrane transporter activity (42)*. An important paralog of this gene is SV2A, which plays a role in the control of regulated secretion in neural and endocrine cells, enhancing selectively low-frequency neurotransmission. Positively regulates vesicle fusion by maintaining the readily releasable pool of secretory vesicles. Receptor for C.botulinum neurotoxin type A (BoNT/A, botA); the toxin probably binds via extracellular loop 4. Recognition by BoNT/A relies on both protein-protein and protein-N-glycosylation; glycosylation of

Asn-559 increases its affinity for BoNT/A. Also serves as a receptor for the closely related C.botulinum neurotoxin type A2; glycosylation is not essential but enhances the interaction. SVAT-associated lncRNAs and mRNAs were found to be differentially expressed in autistic children from the first trimester of pregnancy to delivery (42). Pathologic pregnancies such as spontaneous preterm birth (sPTB), preeclampsia (PE), and gestational diabetes mellitus (GDM) were compared to normal pregnancies, revealing specific correlations between SVAT-lncRNAs and SVAT-mRNAs of STX8, SLC18A2, and SYP with sPTB; SVAT-lncRNAs and SVAT-mRNAs of STX8 with PE; and SVAT-lncRNAs and SVAT-mRNAs of SV2C, as well as SVAT-mRNA of SYP with GDM (42).

Discussion:

Autism Spectrum Disorder (ASD) affects approximately 1% of the global population, presenting challenges in social interaction, communication, repetitive behaviors, and focused interests. The causes of autism remain largely unknown, hindering optimal care for affected individuals. To enhance our understanding of autism, studying postmortem brain tissue is crucial as the pediatric brain is primarily impacted by the disorder. This research provides insights into cellular organization, connectivity, neurotransmitter systems, and brain plasticity, essential for understanding autism's development and potential treatments. Challenges such as limited tissue availability and incomplete donor medical information must be addressed to advance autism research. Recent findings focus on synaptic formation as a key factor in autism pathogenesis, with a dysbalance between excitatory and inhibitory synapses identified as a significant driver. Neurons have distinct membrane domains, including axons and dendrites, which form synapses for communication.

Synaptic formation and Cargo Trafficking

Synapses consist of presynaptic terminals, synaptic clefts, and postsynaptic specializations. Neurotransmitters are released from presynaptic boutons and received by postsynaptic sites through receptors. Different receptors are located at specific regions within the synapse, determining excitatory or inhibitory functions. Molecular components of synapses have been identified through proteomic studies, revealing the recruitment of receptors for synaptic function. Selective localization and transport of synaptic proteins are essential for synapse formation and function. Intracellular trafficking of synaptic cargo involves motor proteinsalong cytoskeletal tracks. The mechanisms responsible for synaptic cargo trafficking are not fully understood, but adaptor molecules play a crucial role in transport specificity. Disruptions in synaptic receptor trafficking may contribute to neurological and psychiatric diseases.Synaptic cargos move bidirectionally in neurons using plus-end and minus-end directed motors along microtubules and can switch between actin and microtubule tracks. The transport of cargo to synaptic sites involves cooperation between different motor proteins for actin and microtubule-based transport. Multiple motor proteins contribute to the transport of AMPA receptors, such as GluA1 binding to myosin V and GluA2 interacting with KIF5. This mechanism allows for quick adjustment and reversal of transport by regulating the activity of different motors attached to a single synaptic cargo. This flexibility enables precise tuning of transport and seamless switching between microtubules and actin, which is crucial for positioning synaptic cargos at specific sites. Additionally, synaptic delivery of AMPA receptors may involve lateral diffusion from extrasynaptic pools to synaptic sites. The cooperation between different motor proteins in synaptic cargo transport raises new questions about motor protein regulation and synaptic cargo docking. Visualizing synaptic cargo transport along single microtubule tracks is challenging due to the unique microtubule organization in dendrites, where microtubules are aligned anti-parallel to each other. To better understand cargo trafficking in dendrites, more research is needed on dendritic microtubule organization and novel approaches to visualize synaptic cargo transport. Understanding the spatial and temporal arrangement of transport complexes and the underlying cytoskeleton is crucial for elucidating how multiple motors regulate specific synaptic cargo transport and delivery.

Role of Syntabulin-Syntaxin 1 A/B Axis

The formation and maintenance of synapses rely on the delivery of synaptic proteins from the soma to distal synapses. Impaired transport may be linked to neurodevelopmental disorders like autism. Syntabulin acts as a motor adapter for kinesin-1 and presynaptic cargos. Syntabulin, classified as piccolo-bassoon-transport vehicle (PTV), regulates neural excitability and controls presynaptic functions. Syntabulin regulates neuronal excitatory and inhibitory imbalance by transporting syntaxin 1 B, more than syntaxin 1A, to the presynaptic membrane. (1). This neurochemical finding is associated with epilepsy in children and could play also an important role in autistic children (1,29).

Defects in syntabulin-mediated transport lead to reduced synapse formation and maturation, contributing to autism-like synaptic dysfunction and social behavioral abnormalities. Syntabulin expression peaks in early postnatal development and declines with brain maturation. Neurons lacking syntabulin show impaired transport, reduced synapse density, altered synaptic transmission, and behavioral abnormalities resembling autism traits. A human missense variant of syntabulin found in an autism patient fails to rescue synaptic deficits in mice lacking syntabulin (45). This important study suggests that impaired transport mechanisms contribute to synaptic dysfunction and behavioral abnormalities in autism (45).In recent studies, an association of the role of syntabulin and its role in autism could be ruled out (29). Especially the exact role of syntaxin 1 A and 1B is of upmost importance in autism spectrum disorders (1,29).

Conclusion:

Further research must focus on the relation of *syntabulin-syntaxin 1A/B axis* in finding the origin of autism in children to open new arenas for pharmaceutical treatment of children with autism spectrum disorder.

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