Syntaxin1A in synaptopathies: From molecular mechanisms to therapeutic implications in neurological disorders (Review)

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Abstract. Syntaxin1A (STX1A) is a presynaptic membrane protein that is abundantly expressed in the central nervous system. It is a key member of the soluble N-ethylmaleimide sensitive factor attachment protein receptor protein family. Notably, STX1A acts as a 'molecular hub' in neural networks by regulating presynaptic membrane fusion with synaptic vesicles and the subsequent release of neurotransmitters. In addition to this function, STX1A is crucial for neuronal development, synaptic plasticity, and ion channel regulation. The deficiency or variation of *STX1A* not only directly disrupts neurotransmitter transmission but also contributes to pathological processes in neurological disorders such as Alzheimer's disease, epilepsy, autism spectrum disorder, and ischemic stroke by interfering with excitatory-inhibitory balance, inducing neuroinflammation, and triggering neuronal apoptosis. The present review summarizes the structure and physiological functions of STX1A, highlights its mechanisms in the pathogenesis of various neurological diseases, and examines its potential as a diagnostic biomarker and therapeutic target for these diseases.

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Abbreviations: STX1A, syntaxin1A; SNARE, soluble N-ethylmaleimide sensitive factor attachment protein receptor; ADHD, attention-deficit/hyperactivity disorder; AD, Alzheimer's disease; ASD, autism spectrum disorder; PD, Parkinson's disease; IS, ischemic stroke; STX1B, syntaxin1B; TMD, transmembrane domain; AZ, active zone; VAMP, synaptobrevin; SM, Sec1/Munc18; Syt1, synaptotagmin-1; DA, dopamine; DAT, dopamine transporter; NE, norepinephrine; NET, norepinephrine transporter; BFNE, benign familial neonatal epilepsy; CSD, cortical spreading depression; 5-HT, 5-hydroxytryptamine; GABA, γ-aminobutyric acid; SNPs, single-nucleotide polymorphisms; Aβ, β-amyloid; GAT-1, γ-aminobutyric acid transporter 1; WS, Williams-Beuren syndrome; MS, multiple sclerosis; AIT, auditory integration training; TLRs, toll-like receptors

Key words: STX1A, neurological disorders, ADHD, ASD, epilepsy, migraine, AD, PD, IS

Contents

1. Introduction

Neurological disorders refer to a diverse group of conditions characterized by neurological damage and functional impairments resulting from structural or functional abnormalities of the central or peripheral nervous systems. Consequently, these neurological disorders include neurodevelopmental disorders, neurodegenerative diseases, and excitatory-inhibitory imbalances, with complex etiologies involving genetic, traumatic, metabolic, infectious, and degenerative factors. Recently, studies have demonstrated that abnormal neurotransmitter release is a common basis for the pathogenesis of various neurological conditions (1,2). Notably, the release of neurotransmitters is a highly coordinated process, with core regulation fundamentally dependent on the assembly and functional stability of the soluble N-ethylmaleimide sensitive factor attachment

protein receptor (SNARE) complex (3). STX1A is a core component of the SNARE complex and is widely expressed in the central nervous system. It is predominantly localized to the presynaptic membrane and is critical for synaptic vesicle fusion and neurotransmitter exocytosis (4). Moreover, research indicates that STX1A regulates the speed and precision of synaptic vesicle fusion (5) and modulates calcium-dependent neurotransmitter release through interactions with accessory proteins such as Munc18-1 and synaptotagmin (6-8). In addition to regulating neurotransmitters, STX1A is involved in synaptic plasticity, neuronal development, and ion channel function. Recent advances in genetics, molecular biology, and neuroimaging have also revealed that abnormal expression, mutations, and disorders of the regulatory mechanisms of the *STX1A* gene are closely linked to various neurological disorders, including neuropsychiatric diseases (9-12), neurodegenerative diseases (13,14) and ischemic stroke (IS) (15). As such, STX1A has emerged as a prominent focus of research in neurological disorders.

The diverse physiological functions of STX1A, along with its dynamic changes under pathological conditions, suggest its potential as a valuable diagnostic biomarker and therapeutic target for neurological disorders. However, current research faces several limitations, including insufficient understanding of disease-specific mechanisms and limited clinical evidence for translation. Therefore, this review systematically outlines the structural features and physiological functions of STX1A. It specifically focuses on recent advances in understanding its role across various neurological diseases.

2. Structure and physiological functions of STX1A

STX1A structure. STX1A is a member of the syntaxin family and is encoded on human chromosome 7q11.23. It comprises 288 amino acids and is one of two isoforms of Syntaxin1, the other being Syntaxin1B (STX1B) (16). STX1A is primarily localized on the plasma membrane. It has four major structural components: An N-terminal peptide (N-peptide), an N-terminal regulatory domain (Habc), a SNARE domain (also known as the H3 domain), and a C-terminal transmembrane domain (TMD) (17) (Fig. 1). The N-peptide is connected to the Habc domain by a flexible region, and the Habc domain is linked to the H3 domain through a linker region. Additionally, the H3 domain is connected to the TMD by a short polybasic juxtamembrane domain. The Habc domain (18) is a highly conserved domain composed of three antiparallel α-helices and plays a crucial role in synaptic transmission in mammals (18). Moreover, the Habc domain interacts with key proteins, including synaptotagmin-1 (Syt1) (19), voltage-gated calcium channels (VGCCs), and Munc18-1, thereby facilitating the precise recruitment of the STX1A-Munc18-1 complex to the active zone (AZ) (20). The SNARE domain of STX1A contains a highly conserved sequence of 60-70 residues with heptanucleotide repeats (21). Significantly, STX1A contributes a Qa-SNARE motif to the SNARE complex, assembling with synaptosomal-associated protein of 25 kDa (SNAP-25; Qbc-SNARE motifs) and synaptobrevin (VAMP; R-SNARE motif) in a 1:1:1 ratio to form a stable four-helix bundle, a structural prerequisite for vesicle fusion and neurotransmitter exocytosis (22). The Habc domain can also interact with its own SNARE motif, forming a 'closed' conformation that regulates STX1A activity, a process modulated by its interaction with neuronal Sec1 (nSec1; also known as rbSec1 or Munc18-1) (23). Furthermore, the C-terminal TMD of STX1A primarily anchors the membrane through its hydrophobic region.

STX1A physiological functions. STX1A is a crucial core protein involved in vesicle fusion, primarily contributing to SNARE complex assembly (24). In mammals, vesicle trafficking is the primary transport mechanism in eukaryotic cells, enabling processes such as endocytosis and exocytosis through membrane fusion. This fusion is facilitated by the formation of SNARE complexes (25). SNARE proteins are categorized based on their membrane localization: t-SNAREs are found on target membranes, while v-SNAREs are located on vesicular membranes. Moreover, VAMP belongs to v-SNARE, while SNAP-25 and STX1A are t-SNAREs (26). The mechanism of plasma membrane vesicle fusion in neuronal cells holds significant physiological importance. Consequently, numerous severe neurological diseases are associated with the improper localization of vesicle fusion-related proteins (27).

In the synapse, a small number of vesicles reside at specific sites in the presynaptic membrane AZ. By contrast, most vesicles are transported to areas near the cell membrane after synthesis, forming a reserve pool. Neurotransmitter release by neuronal exocytosis (Fig. 2) can be divided into several steps, including vesicle mobilization, docking, priming, fusion, and recycling (28). During rest, synaptic vesicles in the readily releasable pool within the AZ participate in neurotransmitter release. In addition, the AZ is enriched in cytoskeletal and scaffold proteins, forming a dense matrix that facilitates the anchoring, preparation, and rapid release of synaptic vesicles. In neuronal and endocrine cells, priming is a necessary rate-limiting step in secretion, in which vesicles are released only after priming. Moreover, SNARE proteins mediate vesicle priming and membrane fusion (29). In the resting state, STX1A is in a 'closed' conformation and cannot participate in the assembly of the SNARE complex. Following an action potential burst, a signal spreads along the axon to the presynaptic membrane, depolarizing the axon. Subsequently, this opens VGCCs, triggering Ca^{2+} influx. Elevated intracellular Ca^{2+} facilitates the recruitment of primed vesicles from the reserve pool to AZ through interactions with Rab proteins (30), RIM, and Munc13. These vesicles are tethered to the plasma membrane, forming trans-SNARE complexes, a process known as vesicle priming (31). The influx of Ca^{2+} binds to synaptotagmin (a Ca^{2+} sensor), with the assistance of the complexin protein, thereby interacting with STX1A to induce an open conformation. Consequently, this promotes SNARE complex assembly through a series of ordered and continuous reactions. In the priming phase, STX1A and SNAP-25 form a t-SNARE complex on the target membrane, which then assembles with VAMP2 (32,33) (on the vesicle membrane), forming a trans-SNARE complex or SNAREpin. This complex forms through a zipper-like mechanism from the N-terminal to the C-terminal regions, pulling the vesicle and plasma membranes into close apposition and providing energy for lipid bilayer fusion (34). Subsequently, primed vesicles are drawn toward the plasma membrane and fuse

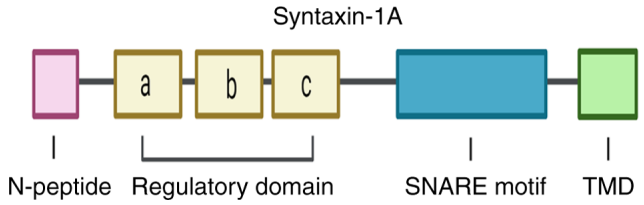

Figure 1. Structure diagrams of syntaxin1A. The N-peptide is shown in red, the Habc domain in yellow, the SNARE motif in blue and the TMD domain in green. This figure was created with BioRender.com.

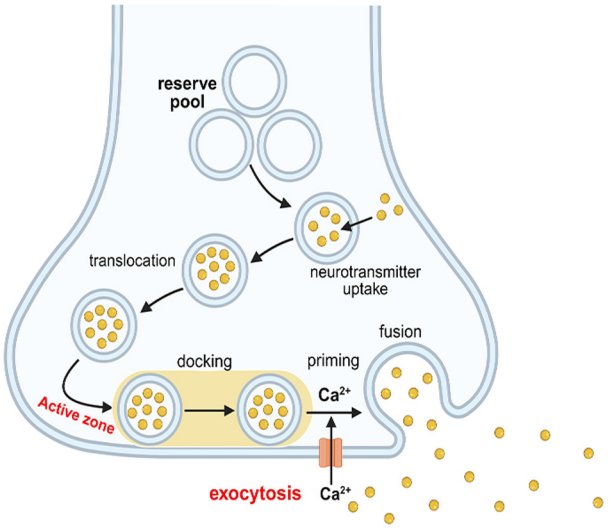

Figure 2. Neuronal exocytosis. Most synaptic vesicles are located within the reserve pool. Upon action potential-evoked calcium influx, vesicles are mobilized to release sites in the active zone. Priming involves the assembly of the SNARE complex and all preparatory steps required for neurotransmitter release. Although priming typically occurs after docking, during sustained exocytosis priming may precede docking, allowing newly arriving vesicles to undergo immediate fusion. This figure was created with BioRender.com. SNARE, soluble N-ethylmaleimide sensitive factor attachment protein receptor.

with it. During this process, the trans-SNARE complex is converted into cis-SNARE complexes, which form a fusion pore and release neurotransmitters from synaptic vesicles into the synaptic cleft (35). In addition, changes in calcium ion concentration directly affect the amount of neurotransmitter released and are necessary for vesicle fusion with the presynaptic membrane (36). Following membrane fusion, the resulting cis-SNARE complexes are disassembled by the AAA+ ATPase NSF (37) and its cofactor α-soluble NSF attachment protein (α-SNAP). This ensures that SNARE can be recycled for the next round of fusion, thereby maintaining the efficiency of synaptic transmission (Fig. 3).

In addition to affecting neurotransmitter release, STX1A plays an indispensable part in neuronal development, synaptic plasticity, and ion channel regulation. Fuschini *et al* (38) demonstrated that STX1A mediates the release of brain-derived neurotrophic factor, thereby regulating neuronal axon growth, synapse formation, and cognitive function. Notably, synaptic plasticity underpins higher neural functions, including learning and memory. As such, research indicates that STX1A plays a significant role in long-term potentiation and low-latency inhibition (39,40). Using the *STX1A* gene-mutation knock-in mouse model, paired-pulse facilitation and enhanced short-term neuronal plasticity (41) have been observed. In the striatum, a previous study has also found that STX1A expression is correlated with the acquisition of dopamine (DA)-related reward learning (42). Furthermore, a preliminary study discovered that STX1A interacts with ion channels (43). Consequently, the two conserved cysteine residues in the transmembrane region of STX1A directly interact with VGCCs, thereby modulating calcium influx and the excitatory coupling of neurotransmitters (44). In addition, STX1A binds to Kv2.1 (a voltage-gated potassium channel) to regulate cellular excitability (45). Thus, these roles suggest that STX1A maintains synaptic activity and functions as a key regulator in neuronal circuit remodeling.

3. STX1A interactions with major accessory proteins

STX1A functions within a precisely coordinated presynaptic protein network. As such, it engages in dynamic interactions with essential accessory proteins, including Sec1/Munc18 (SM) proteins, complexin, and synaptotagmin. Notably, these interactions finely regulate synaptic vesicle fusion and sustain neurotransmitter homeostasis (Fig. 4).

STX1A and SM protein interactions. SM family proteins (46) are essential auxiliary factors in membrane fusion and are involved in nearly all vesicular trafficking events. Munc18-1 (also known as STXBP1) is a key member of the SM family and is the primary regulatory partner of STX1A. It controls vesicle membrane fusion by modulating the conformational states of STX1A as it transitions between open and closed conformations. When Munc18-1 binds to the Habc domain of free STX1A, it stabilizes the monomeric STX1A in a closed, inactive conformation. In this state, the Habc domain interacts with the SNARE motif, forming a closed structure that is enveloped by the arched interface of the domains 1 and 3a of Munc18-1. As a result, this configuration prevents premature SNARE complex formation and inhibits vesicle fusion. Moreover, this mechanism ensures proper STX1A folding and avoids erroneous interactions that could generate off-pathway SNARE assemblies, thereby maintaining the precision of neurotransmitter release. Upon activation by the MUN domain of Munc13, Munc18-1 shifts its interaction to engage the N-terminal region of STX1A. This conformational switch promotes the open state of STX1A, facilitating its assembly with SNAP-25 (47) and VAMP2 (48) into a ternary SNARE complex (49). Finally, Munc18-1 and Munc13 are released from the template complex. Upon doing so, the three SNARE proteins are correctly assembled into a trans-SNARE complex, and membrane fusion is initiated (50). Notably, knockout experiments have shown that Munc18-1-deficient mice exhibit a complete loss of neurotransmitter secretion, despite normal synapse formation, underscoring the indispensable role of Munc18-1 in exocytosis (51).

STX1A and complexin interactions. Complexin (also known as synaphin) is a small cytosolic protein that acts as a clamp during the vesicle fusion process. It contains an N-terminal domain, an accessory α-helix, a central α-helix, and a

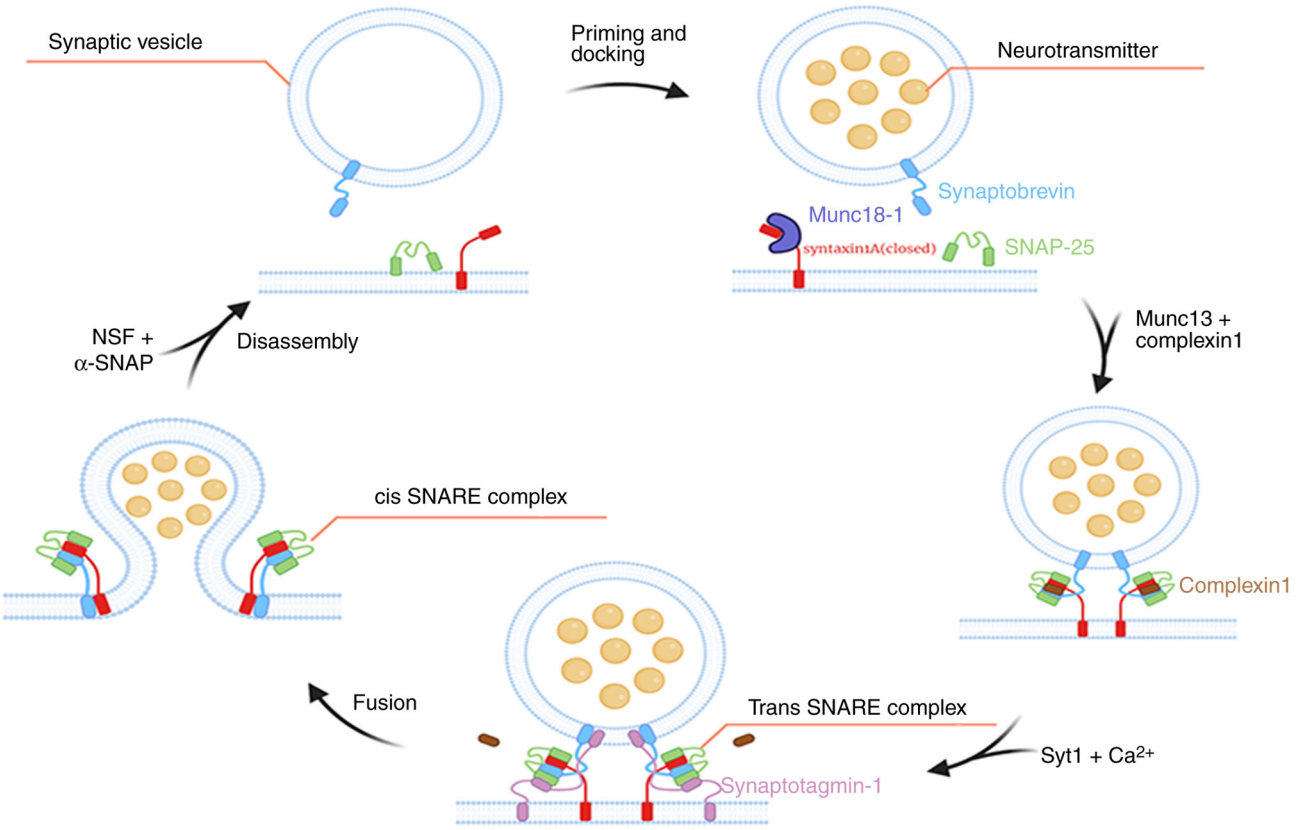

Figure 3. Role of syntaxin1A in the synaptic vesicle circulation. With the assistance of multiple accessory proteins, syntaxin1A regulates the fusion and release of neurotransmitter-containing synaptic vesicles through the formation of the SNARE complex. This figure was created with BioRender.com. SNARE, soluble N-ethylmaleimide sensitive factor attachment protein receptor; NSF, N-ethylmaleimide-sensitive factor; α-SNAP, α-soluble NSF attachment protein; Syt1, synaptotagmin-1; SNAP-25, synaptosomal-associated protein of 25 kDa.

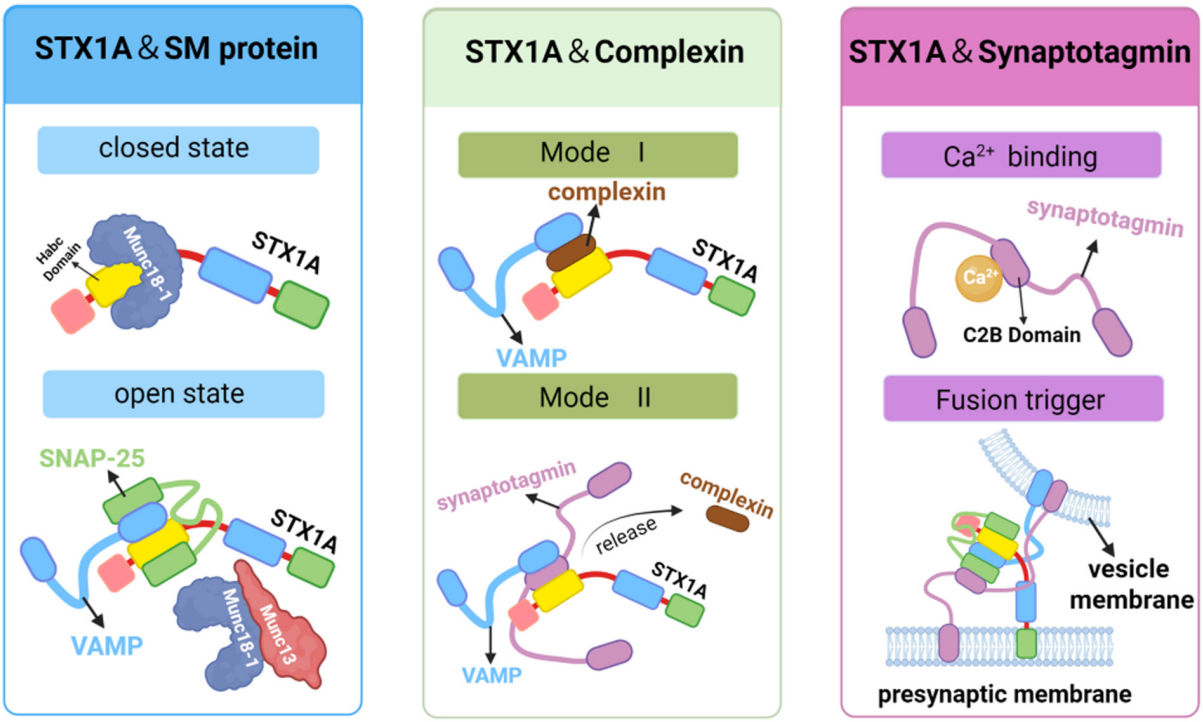

Figure 4. Interactions of syntaxin1A with major accessory proteins. syntaxin1A regulates SNARE complex assembly and vesicle fusion through conformational changes, ensuring precise neurotransmitter release. Munc18-1 prevents premature SNARE assembly, Complexin stabilizes the vesicle in a semi-fused state, and Synaptotagmin triggers fusion upon calcium binding, facilitating neurotransmission. These interactions are crucial for the accuracy of synaptic function and signal transmission. This figure was created with BioRender.com. STX1A, syntaxin1A; SM, Sec1/Munc18; SNAP-25, synaptosomal-associated protein of 25 kDa; VAMP, synaptobrevin.

Table I. Dysfunction and pathogenic mechanism of STX1A in different neurological disorders.

Neurological disorders	STX1A expression	Pathogenic mechanism	(Refs.)
Attention deficit/hyperactivity disorder	Decreased	Dopaminergic disorder and noradrenergic disorder	(9,39)
Autism spectrum disorder	Decreased or increased	Dopaminergic disorder and serotonergic disorder; impaired synaptic plasticity	(73,74,76,79)
Williams-Beuren syndrome	Decreased	Unclear	(81,82)
Epilepsy	Decreased	Glutamatergic disorder	(10,87,90,91)
Migraine	Decreased	Serotonergic disorder and glutamatergic disorder	(59-61)
Alzheimer's disease	Decreased	Synaptic dysfunction	(62,114-117)
Parkinson's disease	Decreased	Dopaminergic disorder	(118-120)
Ischemic stroke	Decreased	GABA transporter 1 disorder	(15,125)
Multiple sclerosis	Decreased	Unclear	(129,130)

STX1A, syntaxin1A; GABA, γ-aminobutyric acid.

C-terminal domain (52). Notably, complexin interacts with STX1A in two distinct modes: i) Mode 1: Complexin-1 (Cpx1), the isoform predominantly expressed in synapses, inserts its central α-helix antiparallel into the groove between VAMP2 and STX1A, stabilizing the vesicle in a semi-fused state and preventing premature fusion. ii) Mode 2: Upon Ca^{2+} binding, Syt1 competes with complexin for binding to STX1A via its C2B domain, relieving the inhibitory effect of complexin and initiating rapid fusion (53).

In complexin-knockdown mice, both spontaneous and evoked neurotransmitter release, including asynchronous and delayed modes, were significantly reduced. This supports the critical regulatory role of complexin in synaptic transmission (54).

STX1A and synaptotagmin interactions. Synaptotagmin is a synaptic vesicle protein evolutionarily conserved across species. It comprises an N-terminal single TMD, an unstructured linker region, and two cytoplasmic protein kinase C-like C2 domains (C2A and C2B) (53). The C2B domain has a high affinity for Ca^{2+} and is primarily responsible for triggering vesicle-plasma membrane fusion. By contrast, the C2A domain contributes to vesicle docking and mobility. Syt1, the principal isoform in synapses, serves as a Ca^{2+} sensor during neurotransmission. Upon Ca^{2+} influx, Syt1 binds phospholipids through its C2 domains, promoting membrane fusion. *In vitro* experiments have shown that Syt1 can dock vesicles by binding to STX1A/SNAP-25 receptor complexes, further emphasizing its central role in Ca^{2+}-dependent neurotransmitter release (55).

4. Association between STX1A and neurological disorders

There is growing evidence that the dysfunction of STX1A is involved in the pathogenesis of various neurological disorders. Additionally, it is closely associated with attention-deficit/hyperactivity disorder (ADHD) (40,56), autism spectrum disorder (ASD) (57), epilepsy (58,59), migraine (60-62), Alzheimer's disease (AD) (63), Parkinson's disease (PD) and IS (Tables I and II) (15).

STX1A and neurodevelopmental disorders. ADHD is a common neurodevelopmental disorder that primarily affects school-age children and adolescents. It is characterized by inattention, hyperactivity, and impulsivity (64). ADHD is suggested to arise from complex interactions among genetic, neurobiological, and environmental factors. Although its exact pathogenesis remains unclear, genome-wide association studies (GWAS) indicate a strong genetic component, particularly involving genes encoding components of the SNARE complex (65). While no single gene has been found to account for ADHD, the interaction between polygenic susceptibility and environmental factors has been proven to increase the risk of ADHD (66). Genetic association studies also provide initial support for a relationship between STX1A and ADHD susceptibility. Wang *et al* (9) found that *STX1A* variations increase susceptibility to ADHD in Chinese Han children. Similar findings have been reported in adult populations, linking *STX1A* polymorphisms to ADHD (67). Furthermore, neuropsychopharmacological evidence suggests that ADHD stems from neurotransmitter system dysfunction (68), particularly imbalances in dopaminergic and noradrenergic systems (40). Furthermore, imbalances in these systems may lead to inattention and hyperactivity.

The most commonly prescribed treatments of ADHD are DA agonists and norepinephrine (NE) agonists, both of which effectively improve the symptoms of ADHD. Given the essential role of STX1A in synaptic vesicle exocytosis, reduced expression may result in insufficient DA release, contributing to ADHD symptoms. Additionally, STX1A regulates DA transporter (DAT) activity, which is responsible for DA reuptake and synaptic clearance (69). Moreover, DAT mediates the reuptake of DA by removing it from the synaptic cleft and returning it to presynaptic neurons. Thus, it modulates the concentration of DA in the synaptic cleft, thereby terminating DA signal transduction and ensuring proper nervous system function. Notably, *STX1A* mutations may exacerbate ADHD by enhancing DAT reuptake (70). Similarly, NE transporter (NET) inhibitors and α2-adrenergic receptor agonists are effective in ADHD treatment. Methylphenidate (MPH) has been shown to

Table II. SNPs of STX1A in various neurological disorders.

Neurological disorders	SNPs	(Refs.)
Attention deficit/hyperactivity disorder	rs3793243, rs875342, rs2293485	(9,65)
Autism spectrum disorder	rs4717806, rs941298, rs4717806	(78,79)
Epilepsy	rs4363087	(87)
Migraine	rs941298, rs2293489, rs6951030	(59-61)
Alzheimer's disease	rs4717806, rs2293489, rs363050	(113)
Multiple sclerosis	rs1569061	(129)

SNPs, single-nucleotide polymorphisms; STX1A, syntaxin1A.

improve the symptoms of ADHD by inhibiting the reuptake of DA and NE through its action on the DAT and NET (71). Atomoxetine (ATX), as a selective NE reuptake inhibitor, is a non-stimulant medication commonly used in clinical practice for the treatment of ADHD. It improves cognitive function by modulating NE and indirectly enhancing DA signaling in the prefrontal cortex (68). A pharmacogenetic study assessed the therapeutic response to immediate-release (IR)-MPH and its association with genes involved in the SNARE complex in the treatment of ADHD. The findings indicated that SNARE complexes mediate the response to commonly prescribed ADHD medications (71). Mishima *et al* (39) also revealed that STX1A modulates noradrenaline transmission by regulating dense-core vesicle secretion, further underscoring its role in ADHD pathogenesis. Notably, the interplay between these two mechanisms may work in concert to ultimately disrupt DA and NE homeostasis, thereby increasing susceptibility to ADHD. Genetic association studies have mostly focused on Chinese Han populations, limiting generalizability (9). However, clinical pharmacological research confirms the functional relevance of the STX1A-associated pathway (68). This implies that modulating presynaptic release capacity influences ADHD treatment outcomes. Consequently, therapies targeting STX1A hold promise for improving the clinical management of ADHD by modulating dopaminergic and noradrenergic systems.

ASD encompasses a range of neurodevelopmental disorders characterized by deficits in social communication, restricted interests, and repetitive behaviors (72). Similar to ADHD, ASD is considered to result from the interplay between genetic predisposition and environmental influences (73). *STX1A*-deficient animal models display behavioral phenotypes analogous to human ASD, such as impaired fear memory, reduced latent inhibition, and abnormal social behavior (74,75). Beyond core ASD symptoms, patients with ASD may also experience central nervous system symptoms such as epilepsy, intellectual disability, and hyperactivity. Moreover, *STX1A* mutations in ASD include splice-site mutations, missense mutations, and frameshift variants, which lead to haploinsufficiency, impaired synaptic plasticity, and dopaminergic and serotonergic [5-hydroxytryptamine (5-HT)] disorders. Recently, Luppe *et al* (10) reported two novel heterozygous missense mutations in *STX1A*, which may perturb SNARE complex assembly or hinder the interaction between STX1A and STX1A-binding proteins. These two patients with epilepsy and ASD features suggest that the dysfunction of STX1A may be the main pathogenic mechanism for some patients with ASD. Notably, it also suggests that ASD shares common pathogenic pathways with epilepsy and ADHD (76). Additionally, Cartier *et al* (77) described a rare ASD-associated hypophosphorylated *STX1A* mutant that reduces DAT-mediated reverse transport and is implicated in ASD pathogenesis. Moreover, abnormalities in serotonergic transmission are common in ASD, and STX1A directly interacts with the serotonin transporter (5-HTT), modulating its localization and function (78). Genetic studies also indicate that *STX1A* polymorphisms, including single-nucleotide polymorphisms (SNPs) rs4717806 and rs941298, are associated with Asperger's syndrome (79). However, these genetic findings do not imply that most ASD cases are driven by *STX1A* defect; the alterations of *STX1A* in ASD show a high degree of heterogeneity. A study in Japan reported elevated *STX1A* mRNA expression in lymphocytes from individuals with high-functioning autism (80). Furthermore, increased *STX1A* expression was observed in the hippocampus of mice prenatally exposed to bisphenol A (BPA), a model for ASD, accompanied by impaired synaptic plasticity (57). Conversely, a study by Al-Ayadhi *et al* (81) investigated the effects of auditory integration training (AIT) in children with ASD. It evaluated changes in plasma STX1A protein levels following the intervention and their correlation with improvements in ASD symptoms (81). The study observed a significant increase in plasma STX1A levels following AIT, accompanied by meaningful enhancements in behavioral, social, and sensory processing scores (81). Thus, STX1A levels may be associated with ASD symptomatology, and plasma STX1A could potentially serve as a diagnostic biomarker for the disorder. Moving forward, restoring or modulating STX1A function in the brain may offer a novel therapeutic direction for ASD.

Notably, reports on STX1A expression in ASD are inconsistent, with both increased and decreased levels described across studies (57,77,80,81). Several factors may account for this discrepancy. At the genetic level, mutations in STX1A exhibit heterogeneity in both genotype and clinical manifestations. Loss-of-function mutations, such as frameshift mutations or splice-site variants that lead to haploinsufficiency) reduce the effective STX1A dosage. By contrast, regulatory variants or compensatory responses may yield apparent upregulation at the mRNA level. From a biological perspective, STX1A expression is highly dependent on

environmental factors. It varies across brain regions (such as the frontal lobe and hippocampus), cell types (including excitatory and inhibitory neurons), and critical windows of neural development. Moreover, most studies use peripheral tissues or homogenate samples, which cannot capture this spatial and cell-specificity. Furthermore, technical limitations, such as the imperfect correlation between mRNA levels and functional protein activity, and confounding environmental exposures (such as BPA), introduce additional variability across studies. Consequently, the reported inconsistencies reflect not contradiction but rather the interplay of genetic heterogeneity, clinical heterogeneity, and methodological limitations. Thus, future studies integrating genotype-stratified cohorts, highly specific transcriptomics, and functional validation are needed to elucidate the role of STX1A across subtypes of ASDs.

Williams-Beuren syndrome (WS) is a rare genetic neurodevelopmental disorder characterized by a hemizygous deletion at 7q11.23. WS can affect multiple systems, particularly the nervous, cardiovascular, endocrine, and digestive systems. It leads to clinical manifestations of neurological abnormalities such as intellectual disability, excessive sociability, and attention-deficit. Notably, the STX1A gene, within the WS critical region, has been identified as a strong candidate for WS and may play a significant role in the neurodevelopment of the disease (82). A previous study demonstrated that STX1A gene transcript levels were significantly correlated with intellectual functioning in patients with WS (83). However, current research on STX1A in WS remains limited. Moreover, its precise pathogenic mechanism remains unclear.

STX1A and epilepsy. Epilepsy is a common heterogeneous neurological disorder, whose main feature is the abnormal discharge of neurons leading to recurrent, paroxysmal, and transient dysfunction of the central nervous system (84). In the past decade, growing evidence has highlighted the pivotal role of synaptic protein-encoding genes in epilepsy pathogenesis (85). Among these, pathogenic variants affecting the SNARE complex and its regulatory proteins have been incorporated into the emerging concept of 'SNAREopathies' (SNARE-related disease spectrum), which helps explain epilepsy and other neurodevelopmental disorders arising from impaired presynaptic release mechanisms (86,87). While both isoforms, STX1A and STX1B, play roles in vesicle fusion, they exhibit distinct expression patterns. In knockout mouse models, *STX1A* and *STX1B* exhibit partial functional compensation. However, double knockout of these isoforms results in embryonic lethality due to the complete loss of synaptic vesicle fusion (18). Notably, the role of *STX1B* gene mutations in epileptic seizures has been extensively studied (87). By contrast, research on the association between *STX1A* mutations and the development of epilepsy is relatively limited. Recent human genetic studies have provided direct support for the association between *STX1A* and epilepsy. In 2023, Luppe *et al* (10) reported that a missense mutation in the *STX1A* gene leads to *STX1A*-related developmental and epileptic encephalopathy (10). In addition to rare variants, population-based genetic studies have identified statistical associations between common STX1A polymorphisms and cryptogenic epilepsy (88). For instance, in a North Indian population, SNPs in *VAMP2* and *STX1A* were associated with cryptogenic epilepsy (88). However, broader population-level validation of these associations remains limited.

Experimental and clinical evidence further suggests that STX1A may contribute to epileptogenesis by modulating excitatory neurotransmission and neuronal excitability. Notably, dysregulation of glutamatergic signaling represents a key mechanism underlying seizure generation (89), indicating that disruption of presynaptic release machinery alters excitatory synaptic strength. A previous study using septic rat models revealed a significant reduction in STX1A and Munc18-1 expression in the hippocampus, correlating with impaired glutamate release (90). Another study demonstrated that STX1A reduces cell surface expression of the glutamate transporter excitatory amino acid carrier 1 (EAAC1), thereby inhibiting glutamate uptake and potentially contributing to seizure susceptibility (91). In addition, regulation of ion channels has been implicated in epilepsy pathophysiology. Benign familial neonatal epilepsy (BFNE) is commonly caused by mutations in voltage-gated potassium channels (KCNQ2 and KCNQ3). Soldovieri *et al* (92) were the first to identify dysfunctional STX1A-channel interactions in BFNE, where mutant *STX1A* fails to regulate potassium channel activity. Consequently, mutations in these channels reduce M-type K^+ currents, leading to neuronal hyperexcitability. STX1A binding to K^+ channels affects these M-currents (93) and *STX1A* dysfunction may exacerbate the effect. Another study suggested that STX1A-related epileptic encephalopathy is not only characterized by STX1A dysfunction but may also manifest as dysfunction of its binding partner STXBP1 (encoding Munc-18) (94). This indicates that the epileptic phenotype may result from the destruction of a broader presynaptic release network rather than from the action of STX1A alone. This is consistent with the 'SNAREopathies' pathological mechanism, emphasizing co-aggregation impairment of presynaptic secretory pathways as a common pathogenic mechanism in epilepsy and neurodevelopmental disorders.

STX1A and migraine. Migraine is a common neurovascular disorder characterized by recurrent headaches, often accompanied by sensory disturbances such as photophobia and phonophobia (95,96). Its global prevalence is higher in females than in males, reflecting contributions from hormonal, genetic, and neurobiological factors. From a genetic standpoint, migraine exhibits a typical complex polygenic architecture, as supported by additional transcriptomic and functional analyses. For instance, a large-scale GWAS identified 123 susceptibility loci and mapped STX1A to one of the implicated regions (97). This finding was further confirmed in studies by Felício *et al* (98,99). Furthermore, research by Quintas *et al* (62) indicates that the STX1A gene is associated with migraine susceptibility and is an essential candidate gene for migraines (100). This result has also been confirmed in case-control studies conducted in Portugal (62) and Spain (61). These findings suggest a strong genetic association between STX1A and migraine, but mechanistic investigations into how STX1A variants contribute to migraine pathophysiology remain scarce.

The leading pathophysiological hypotheses of migraine involve cortical spreading depression (CSD), dysfunction of serotonergic and glutamatergic neurotransmission, and

neurogenic inflammation (101-103). Recent research has also emphasized the critical role of neurotransmitter systems in migraine pathogenesis (1). In particular, the serotonergic system plays a key role in pain modulation. Consequently, reduced serotonin levels can exacerbate CSD and contribute to the onset of migraine attacks. Clinically, triptans, selective 5-$HT_1B/_1D$ receptor agonists, have proven highly effective in treating migraine (104,105), supporting the central role of serotonin. Therefore, *STX1A* mutations that reduce serotonin release may represent a potential mechanism for migraine development.

In parallel, glutamate and its receptors have also been implicated in migraine in both pediatric and adult populations (106,107). Epidemiological studies indicate a high comorbidity between migraine and epilepsy. This is especially true in women, individuals with temporal lobe epilepsy, or those who experienced seizures within three months of a migraine diagnosis (108,109). These findings suggest a shared excitatory pathophysiology between the two disorders (110), potentially involving STX1A-mediated regulation of glutamatergic transmission. Excessive glutamate release can also activate N-methyl-D-aspartate receptors and trigger CSD, a neurobiological substrate of migraine aura, thereby promoting trigeminovascular activation and central sensitization, which ultimately culminate in headache (107). It is hypothesized that STX1A modulates excitatory neurotransmission, thereby participating in the pathogenesis of both epilepsy and migraine. Given its involvement in regulating excitatory neurotransmitter release, STX1A could serve not only as a genetic risk factor but also as a potential therapeutic target in migraine. Moreover, its polymorphisms may function as disease-specific biomarkers (100).

STX1A and neurodegenerative diseases. AD is the most common form of neurodegenerative disorders, characterized primarily by progressive memory loss and cognitive decline (111). Its hallmark pathological features include extracellular accumulation of β-amyloid (Aβ) forming neuritic plaques and intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein. According to previous studies, synaptic dysfunction and loss of synaptic plasticity are the fundamental pathological processes in the early stages of a variety of neurodegenerative diseases (112-114). STX1A, as a necessary presynaptic t-SNARE protein, is crucial for the secretion of synaptic vesicles. At the protein and transcriptional levels, STX1A is commonly associated with AD. Proteomic analysis of the prefrontal cortex in patients with AD revealed significantly reduced STX1A levels compared with healthy controls (115). A previous large-scale targeted proteomic study has further revealed that the level of STX1A in patients with AD is positively correlated with cognitive function. By contrast, a negative correlation was found with AD pathological burden. In cognitively impaired individuals, the reduction in STX1A may be more pronounced than that in STX1B (116). Collectively, these findings provide strong evidence linking STX1A loss to AD-related cognitive vulnerability. Complementary transcriptomic data further support the concept that synaptic release pathways are disrupted in AD. Significant downregulation of *STX1A* gene expression was observed in the brains of an AD mouse model and Dp16 mice, which may be a decisive factor in AD-related cognitive decline (117). In addition, emerging cerebrospinal fluid proteomic studies in genetically AD cohorts suggest that proteins involved in synaptic and vesicle cycling pathways exhibit alterations early in the disease course (118). Moreover, Aβ oligomers (a neurotoxic agent) are primary contributors to the pathological process of AD, with the capability of damaging neurons through a variety of mechanisms. Experimental research has also demonstrated that Aβ oligomers directly bind to the SNARE motif of STX1A, thereby inhibiting SNARE complex formation and blocking exocytosis (63). This disruption of synaptic transmission is proposed as an additional potential mechanism by which STX1A contributes to cognitive deficits in AD. However, given the essential and widespread role of STX1A in neurotransmission, directly targeting STX1A carries potential safety concerns, as it could broadly disrupt synaptic release across neurons. Thus, therapeutic strategies may be better directed toward selectively blocking pathological Aβ-STX1A interactions, thereby restoring SNARE-mediated exocytosis and delaying or reversing cognitive decline in AD while minimizing adverse effects. Current therapeutic approaches for AD remain limited in efficacy; therefore, elucidating the role of STX1A could offer new avenues for treatment development.

PD is a chronic neurodegenerative disease characterized by progressive movement disorders. The basic pathological features of PD are the misfolding and abnormal aggregation of α-synuclein (α-Syn) and the loss of dopaminergic neurons in the substantia nigra. Notably, the SNARE complex is also involved in PD pathogenesis (13). Xiong *et al* (119) observed downregulated STX1A expression in a PD rat model, suggesting that impaired presynaptic release capacity may accompany dopaminergic disorder. Furthermore, patients with PD exhibited elevated α-Syn levels in serum exosomes along with higher clinical scores compared with healthy controls (120). Notably, Agliardi *et al* (121) also identified a negative correlation between α-Syn and STX1A levels in the serum exosomes of patients with PD. Therefore, these studies suggest an inverse relationship between α-Syn burden and presynaptic STX1A integrity. Collectively, STX1A may serve as a biomarker of presynaptic vulnerability in PD diagnosis.

STX1A and IS. IS is the most prevalent type of stroke and ranks as the third leading cause of death and disability worldwide. Previous research has reported significant upregulation of STX1A protein levels in the brains of IS rat models, including elevated expression in blood samples from patients with IS (122). These findings suggest that STX1A may serve as a potential clinical biomarker for stroke prognosis. Additionally, elevated levels of γ-aminobutyric acid (GABA) during the subacute phase of IS activate extra-synaptic GABA receptors, leading to tonic inhibition that suppresses post-stroke neuronal excitability and hinders recovery (123-125). GABA transporter 1 (GAT-1) plays a vital role in the reuptake of extracellular GABA, enhancing neuronal excitability and facilitating recovery after stroke. Lin *et al* (15) discovered that IS induces GAT-1-STX1A interaction, leading to GAT-1 dysfunction in the subacute phase. In a mouse model of stroke, administration of ZLQ-3 (a small-molecule inhibitor that disrupts the GAT-1-STX1A interaction) dissociated the GAT-1-STX1A interaction,

successfully restored GAT-1 function, and enhanced GABA reuptake. This mechanism not only increased cortical excitability but also strengthened GABAergic synaptic inhibition, ultimately promoting functional recovery post-stroke (15). Thus, STX1A is a novel therapeutic target for enhancing post-stroke neurorehabilitation.

In addition, Kv2.1 (a voltage-gated K^+ channel) plays a key role in regulating cell excitability and is also vital following IS. Evidence indicates that Kv2.1 can interact with STX1A to promote K^+ efflux, thereby contributing to central neuronal apoptosis (126). *In vitro* studies have shown that disrupting the Kv2.1-STX1A interaction significantly reduces K^+ efflux, exerting neuroprotective effects (45,127). Another study demonstrated that open-conformation STX1A appears to inhibit Kv channel-mediated K^+ currents (128), suggesting that this mechanism could be leveraged for neuroprotection.

STX1A and multiple sclerosis (MS). MS is a common autoimmune disease of the nervous system. Its primary manifestation is chronic inflammation that destroys myelin in the white matter of the brain, leading to demyelinating disorders and progressive neurological dysfunction. With advances in research, MS is no longer regarded as a purely white matter demyelinating disease. Gray matter pathology and synaptic dysfunction have also been increasingly recognized (129). Notably, these alterations may contribute to MS-associated cognitive impairment and neuropsychiatric manifestations. A recent study conducted in Turkish populations found a significant association between *STX1A* gene polymorphisms and increased MS susceptibility (130). By contrast, similar associations were not observed in German or Egyptian populations (131). This discrepancy suggests that STX1A is unlikely to represent a universal, cross-population driver of MS pathogenesis, but may instead function as a modest, context-dependent genetic modifier.

5. Potential links between STX1A, neuroimmune regulation, and the gut-brain axis

With continued advances in neuroscience research, the pathophysiological mechanisms underlying neurological disorders are no longer considered limited to simple neurotransmitter imbalances. Instead, new evidence highlights the intricate interplay between neuroinflammation and the gut-brain axis as critical contributors to central nervous system homeostasis and disease progression (132). Immune mediators, particularly toll-like receptors (TLRs) and cytokines, are now recognized as key modulators of neural function (133). In addition, the gut microbiota has emerged as an important regulator of central nervous system activity (134). Although the present review primarily focuses on the role of STX1A in synaptic transmission, it is increasingly important to consider its potential links with neuroimmune signaling and gut-brain axis dynamics.

Neuroinflammation represents an intrinsic immune response of the central nervous system to injury, infection, or pathological insults. It is primarily mediated by glial cells, including microglia and astrocytes. TLRs, which belong to the family of pattern-recognition receptors, are widely expressed on glial cells and detect pathogen-associated molecular patterns and damage-associated molecular patterns, thereby initiating inflammatory signaling cascades. Activation of TLR pathways leads to the release of pro-inflammatory cytokines, such as interleukin-1β (IL-1β), which have been demonstrated to modulate neuronal function and synaptic plasticity. Additionally, members of the IL-1 cytokine family play central roles in neuroinflammatory processes, and genetic polymorphisms within these genes can influence the magnitude and duration of inflammatory responses, thereby shaping susceptibility to neurological disorders (135). Moreover, dysregulated TLR signaling has been implicated in protective and pathogenic immune responses across diverse disease contexts, underscoring its dual role in immune-mediated tissue homeostasis and injury (136,137). Given that STX1A is a core component of the SNARE complex directly involved in neurotransmitter release, inflammatory microenvironments may influence its function by altering STX1A expression, post-translational modification, SNARE complex assembly, or synaptic plasticity.

In parallel, the gut microbiota interacts bidirectionally with the central nervous system through neural, endocrine, immune, and metabolic pathways. This is collectively referred to as the gut-brain axis. Microbiota-derived metabolites, microbially produced neurotransmitters, and microbiome-mediated modulation of host immunity can exert long-range effects on brain function and behavior (138). Dysbiosis of the gut microbiota has been closely associated with the onset and progression of numerous neurological disorders (133,139). Disruption of microbial homeostasis can compromise intestinal barrier integrity, increase gut permeability, and permit translocation of microbial products into the systemic circulation, thereby triggering systemic and neuroinflammatory responses (140). Consequently, such gut-driven inflammatory processes may profoundly affect the central nervous system by reshaping neurotransmitter systems, inducing neuroinflammation, and impairing synaptic integrity, ultimately exerting indirect effects on STX1A-dependent synaptic function.

At present, direct interactions between STX1A and immune mediators or gut microbiota-derived factors remain largely unexplored. Nevertheless, the evidence outlined above supports the existence of an indirect regulatory framework linking STX1A-mediated synaptic transmission to neuroimmune and gut-brain axis signaling. Thus, a deeper understanding of these interconnections may open novel avenues for therapeutic strategies targeting neuroimmune pathways or the gut-brain axis, with the potential to improve clinical outcomes in STX1A-associated neurological disorders.

6. Mechanistic and translational implications of STX1A in neurological disorders

Recently, the view that synaptic structural and functional deficits constitute a key factor in neurological diseases has gained widespread acceptance. Disorders arising from such synaptic dysfunctions are collectively referred to as synaptopathies, including ADHD, ASD, epilepsy, migraine, AD, PD, schizophrenia, as well as other disorders. Thus, these underlying diseases may share a common pathogenic mechanism and genetic basis. Notably, most research indicates that SNARE complexes play a significant role in maintaining the structure and function of synapses (58). Acting as a ‘molecular hub’

within neural networks, STX1A contributes to synaptopathies through multiple mechanisms, including regulation of SNARE complex assembly, coupling to accessory proteins and transporters, and interactions with ion channels (42).

Across neurodevelopmental disorders (such as ADHD) and neurodegenerative diseases (such as PD), STX1A may participate in pathophysiology by mediating dopaminergic dysfunction. However, the underlying mechanisms are fundamentally distinct. In ADHD, STX1A dysregulation may impair synaptic vesicle exocytosis, reduce dopamine release in prefrontal-striatal circuits, and enhance dopamine clearance, thereby contributing to cognitive and behavioral symptoms (67). By contrast, STX1A-related dopaminergic impairment in PD occurs in the context of progressive degeneration of nigrostriatal dopaminergic neurons and aberrant α-Syn-SNARE interactions (141,142). Under these conditions, alterations in STX1A are more likely to reflect the vulnerability and declining function of surviving presynaptic terminals rather than serve as an isolated driver of neurotransmitter imbalance. Thus, although both disorders exhibit dopaminergic abnormalities, their mechanistic bases, and consequently their translational implications, differ substantially.

Future studies should explore therapeutic strategies that selectively disrupt pathological STX1A-DAT coupling to restore dopaminergic signaling in ADHD. By contrast, PD-associated changes in STX1A may be more valuable as a biomarker of synaptic integrity and presynaptic reserve, enabling more accurate, cost-effective, and minimally invasive assessment of disease progression and treatment response.

In addition, a spectrum of neurological syndromes arising from mutations in SNARE-related genes that disrupt SNARE complex composition and function is collectively referred to as 'SNAREopathies' (86). Neurodevelopmental disorders caused by STX1A fall within this disease spectrum and, together with other SNARE-associated genes, contribute to disease severity, phenotypic variability, and age at onset. Mutations in STXBP1, a master regulator required for STX1A stabilization and SNARE complex initiation, typically result in severe developmental and epileptic encephalopathies (143). As such, this reflects the catastrophic consequences of early failure in SNARE assembly. Similarly, SNAP25, a core Qbc-SNARE that directly drives membrane fusion, is associated with profound synaptic release defects and early-onset neurodevelopmental phenotypes when pathogenic variants are present (144). By contrast, STX1A occupies a more modulatory and integrative position within the SNARE complex. Owing to its partial functional redundancy with STX1B, STX1A dysfunction more often manifests as synaptic vulnerability rather than complete failure of vesicle exocytosis (17). Furthermore, STX1A-associated disorders tend to display selective effects on neurotransmitter release within specific neuronal populations and often present with a relatively later onset (10). Notably, this markedly contrasts the severe and uniform phenotypes characteristic of core SNAREopathies (86).

Overall, elucidating the physiological and pathophysiological roles of STX1A may serve as a critical bridge between classical SNAREopathies and other complex synaptopathies. Such an approach offers novel insights into the mechanistic continuum linking rare presynaptic release disorders with polygenic risk for common neurological diseases.

7. Conclusion and future perspectives

Over the past several decades, our understanding of the structure and physiological functions of STX1A has significantly advanced. As a key mediator of neuronal exocytosis, STX1A interacts with VAMP and SNAP-25 to form the core SNARE complex. This complex is essential for the docking and fusion of synaptic vesicles with the presynaptic membrane, positioning STX1A as a central component in synaptic transmission. The functional dynamics of STX1A, including its conformational shifts between open and closed states, its role in SNARE complex assembly, and its interactions with various regulatory proteins, are crucial for regulating its function.

It can be concluded that STX1A plays a crucial role in major neurological diseases, making it a vital target for their diagnosis and treatment. By regulating the release of neurotransmitters, including glutamate, GABA, 5-HT, DA, and NE, STX1A influences both the progression of these diseases and the recovery of nervous system function. Genetic studies have strongly indicated that mutations and dysregulation of *STX1A* are linked to various neurological diseases such as ADHD, ASD, epilepsy, migraine, AD, PD, and IS. Additionally, aberrant STX1A expression can impair SNARE complex formation and disrupt the release of essential neurotransmitters, resulting in cognitive, behavioral, and neuronal signaling deficits. Since normal brain function relies on a precise balance of neurotransmitter activity, any disturbance in STX1A expression can lead to significant neurological dysfunction.

To date, most research on the *STX1A* gene has focused on its expression and polymorphisms. However, its potential as a pharmacological target remains largely underexplored. While proteomic and genomic studies have linked *STX1A* to various diseases, including AD, ADHD, ASD, IS, and epilepsy, its role in other neurological disorders has yet to be fully elucidated. Further investigation into the mechanisms by which *STX1A* contributes to neurological diseases could lead to the identification of novel therapeutic strategies.

The targeted therapeutic strategy exemplified by ZLQ-3 in ischemic stroke, namely, selectively disrupting pathological STX1A protein interactions to restore synaptic balance without globally impairing neurotransmitter release, may be extendable to other neurological disorders. In AD, Aβ oligomers have been shown to directly bind the SNARE motif of STX1A, thereby inhibiting SNARE complex assembly and synaptic vesicle exocytosis. Rather than directly targeting STX1A, peptide-based competitors that selectively block the pathological Aβ-STX1A interaction may represent a safer and more feasible alternative. Future studies could focus on designing short peptides that competitively occupy the binding interface, followed by protein modification strategies to enhance blood-brain barrier penetration and molecular stability, enabling targeted delivery while minimizing peripheral side effects.

In addition, in neurological conditions driven by aberrant overexpression of STX1A, such as certain subtypes of ASD, gene-silencing approaches may be worth consideration. The design of STX1A-specific siRNAs or miRNA mimics targeting the 3'-untranslated region, delivered to defined brain regions via lipid nanoparticles or viral vectors, could theoretically normalize excessive STX1A expression.

Nevertheless, the development of STX1A-targeted therapies remains a substantial challenge. This includes limited blood-brain barrier permeability, the ubiquitous presynaptic distribution of STX1A, and the risk of disrupting global neurotransmitter homeostasis. Taken together, indirect modulation of STX1A function may represent a more practical and safer therapeutic strategy. Approaches that selectively interfere with disease-specific protein interactions or downstream pathways appear especially promising. Accordingly, future research should prioritize precision-targeting approaches that restore synaptic function while preserving the essential role of STX1A in neuronal communication.

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Competing interests

The authors declare that they have no competing interests.

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