Neurochemistry International 122 (2019) 196–207

Contents lists available at ScienceDirect

Neurochemistry International

journal homepage: www.elsevier.com/locate/neuint

Neuronal SNARE complex: A protein folding system with intricate protein-protein interactions, and its common neuropathological hallmark, SNAP25

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ARTICLE INFO

Keywords:
SNARE complex
Protein folding
SNAP25
Neurological disorders
Protein aggregation

ABSTRACT

SNARE (Soluble NSF(N-ethylmaleimide-sensitive factor) Attachment Receptor) complex is a trimeric supramolecular organization of SNAP25, syntaxin, and VAMP which mediates fusion of synaptic vesicles with the presynaptic plasma membrane. The functioning of this entire protein assembly is dependent on its tetrahelical coiled coil structure alongside its interaction with a large spectrum of regulatory proteins like synaptotagmin, complexin, intersectin, etc. Defects arising in SNARE complex assembly due to mutations or faulty post-translational modifications are associated to severe synaptopathies like Schizophrenia and also proteopathies like Alzheimer's disease. The review primarily focuses on SNAP25, which is the prime contributor in the complex assembly. It is conceptualized that the network of protein interactions of this helical protein assists as a chaperoning system for attaining functional structure. Additionally, the innate disordered nature of SNAP25 and its amyloidogenic propensities have been highlighted employing computational methods. The intrinsic nature of SNAP25 is anticipated to form higher-order aggregates due to its cysteine rich domain, which is also a target for several post-translational modifications. Furthermore, the aberrations in the structure and expression profile of the protein display common patterns in the pathogenesis of a diverse synaptopathies and proteopathies. This work of SNARE literature aims to provide a new comprehensive outlook and research directions towards SNARE complex and presents SNAP25 as a common neuropathological hallmark which can be a diagnostic or therapeutic target.

1. Introduction

Supramolecular assemblies of proteins, as an evolutionary innovation, are distributed across the biological system to execute complex functions. One such magnificent protein assembly is the neuronal SNARE (**S**oluble **N**SF(N-ethylmaleimide-sensitive factor) **A**ttachment **RE**ceptor) complex (with ring complexes ranging from 15 to 300 nm in diameter) which plays a central and fundamental role in neuronal signaling (Cho et al., 2005). The assembly is regulated by an intricate network of protein-protein interactions and can be considered as an upshot of complex protein folding and organization. SNARE proteins constitute a large clade with homologous members distributed across yeasts and mammalian cells (Advani et al., 1998; Burri and Lithgow, 2004). Their principal function in the synaptic event is to mediate neuron-neuron communication by a process where Synaptic Vesicles (SVs) fuse with the presynaptic plasma membrane (PM) in a Ca^{2+} triggered mechanism leading to neurotransmitter release (illustrated in Fig. 1) (Chen et al., 1999). Therefore, the importance of this hydrophobic supramolecular assembly lies in driving neuronal signaling and proper functioning of the overall psycho-physiological system. Anomaly in the expression and core structure of SNARE proteins and subsequent destabilization of the same, implicate in a number of aberrant neurological conditions like Schizophrenia (SCZ), Bipolar disorder (BD), Attention Deficit Hyperactivity Disorder (ADHD), and Autism Spectrum Disorder (ASD) etc. (Cupertino et al., 2016; McNew et al., 2000; Söllner et al., 1993).

The minimal core of SNARE complex (illustrated in Fig. 1) as identified by Fasshauer et al. consists of three alpha-helical proteins, namely, (i) SNAP25 (synaptosomal-associated protein 25), a presynaptic PM-anchored protein, (ii) syntaxin, a presynaptic PM-integral protein, and (iii) synaptobrevin (Sb) or VAMP (Vesicle Associated Membrane Proteins), a vesicle-trans-membrane protein (Fasshauer

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https://doi.org/10.1016/j.neuint.2018.12.001
Received 2 July 2018; Received in revised form 8 November 2018; Accepted 1 December 2018
Available online 02 December 2018
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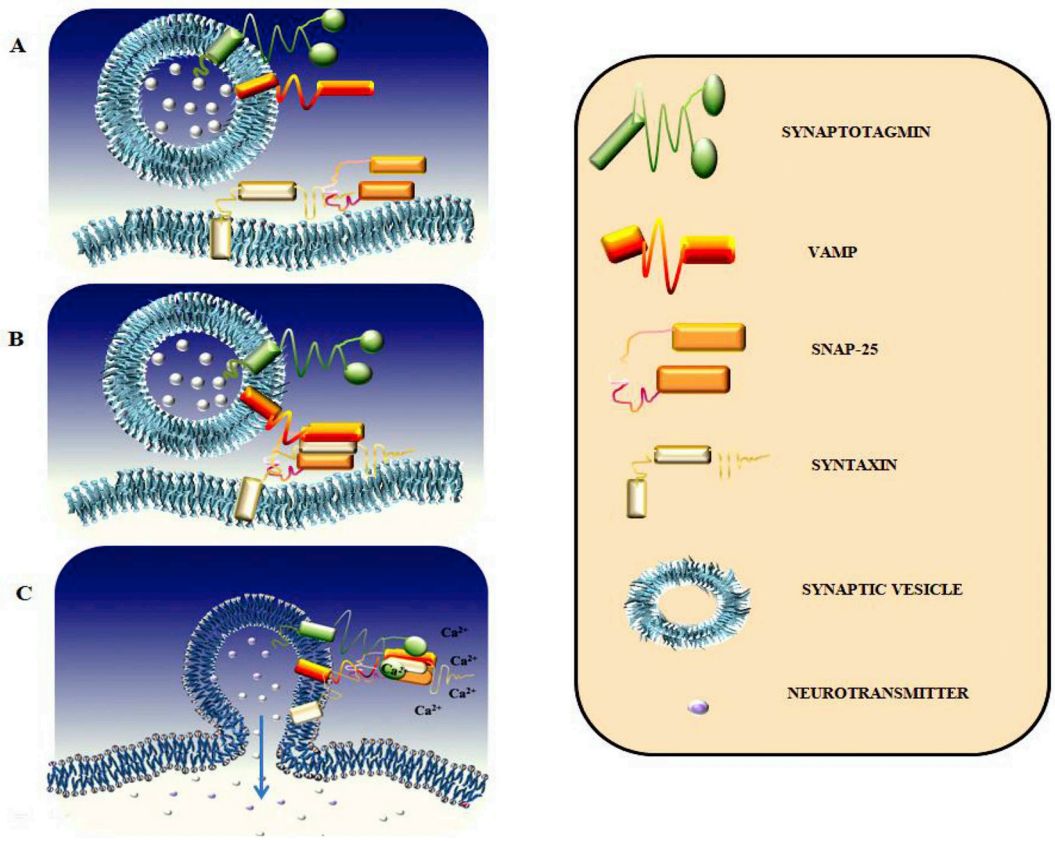

Fig. 1. Neurotransmitter containing Synaptic Vesicle (SV) near the presynaptic plasma membrane (A); SNARE Complex formation between SV transmembrane protein VAMP and plasma membrane proteins, SNAP25 and syntaxin (B); Ca^{2+} binds to synaptotagmin leading to membrane fusion and neurotransmitter release (C).

et al., 1998; McNew et al., 2000). The three dimensional (3D) organization of SNARE complex was found to be tetrahelical coiled-coil parallel bundle (Poirier et al., 1998), wherein, SNAP25 contributes two alpha-helices and the other two helices are contributed by VAMP and syntaxin, respectively (Sutton et al., 1998). Other than these core proteins, interacting partners of SNARE complex or SNARE interactors like N-ethylmaleimide sensitive factor (NSF), complexin, neurogulin, intersectin, etc. play an important regulatory role in the entire neurotransmission process through a Ca^{2+} triggered process (Chang et al., 2018; Chen et al., 1999; Zhou et al., 2017). A comprehensive list of the core components of SNARE complex and some of the regulating interactors is enumerated in Table 1(a) and 1(b). The understanding of SNARE complex is becoming increasingly complicated with ongoing discoveries of interactors, which chaperone the 3D organization of this exquisite molecular apparatus. Thus, SNARE complex has come up as a sensitive supramolecular multimeric assembly and an intricate network of protein interactions. Indeed, the disruption of this delicate system severely implicates to synaptic dysfunction and neurodegeneration.

Of particular concern, the link between an irregularity introduced in brain physiology at the molecular level and the distortion of the psychological behaviour has yet not been elucidated well. We, therefore believe, a review portraying a molecular view of SNARE constituents and the implication of their aberrant organization in neuropathology is essential. SNAP25, the principle contributor to the structural organization of SNARE complex, is primarily focused in this review. The abnormal expression of SNAP25 in a number of neurological and neurodegenerative diseases is hypothesized that this helical protein might be a common neuropathologcial marker. In this direction, the present work attempts to identify a link between the intrinsic nature, aggregation propensity and the structural aberration of SNAP25 in SNARE complex assembly.

2. SNAP25: structure and function

2.1. Structure of SNAP25

SNAP25 was first identified by Oyler et al. and was found to be differentially expressed in the neuronal subpopulations (Oyler et al., 1989). Further, it was reported that it consists of two isoforms (SNAP25a and SNAP25b), which arise due to alternative splicing of the duplicated Exon 5. These isoforms were found to differ in 9 amino acids out of 39 from the mutually exclusive Exon (5a and 5b) (Bark, 1993). Interestingly, these SNAP25 isoforms are differentially expressed at different stages of neurodevelopment, wherein, 25a is majorly expressed at the embryonic stage and 25 b at the postnatal life (Bark et al., 1995). Subsequent discoveries confirmed that this developmental trend is conserved in humans as well (Prescott and Chamberlain, 2011). Structurally, SNAP25 (206 amino acids/25 kDa) is a helical protein which contributes two helices in the tetrahelical coiled coil structure of SNARE complex (other two helices are contributed by syntaxin and VAMP). Fig. 2(A) represents the truncated 3D structure of SNARE complex (PDB code: 3RK2) showing the tetrahelical coiled coil organization (structural view in hydrophobicity scheme). As seen from the figure, all SNARE proteins contain alternating hydrophobic and hydrophilic patches, which is indicative of intrinsic amyloidogenic propensity (Broome and Hecht, 2000). Fig. 2(B) represents the 3D structure of SNAP25 generated using homology modelling in Phyre2 software (Kelley et al., 2015). The generated 3D model showed that a large portion of the protein is intrinsically disordered. This aspect of SNAP25 is also common to amyloid-β (Aβ) and α-synuclein, which are associated to the proteopathies, Alzheimer's and Parkinson's, respectively (Choi et al., 2011). This provokes the speculation that SNAP25 might also misfold and aggregate. Fig. 2(C) is the predicted secondary

Table 1a
Core components of the SNARE complex, their properties and associated diseases.

Proteins	Structural feature/Properties	Mol.wt. (kDa)	Molecular function	Diseases	References
SNAP25	• Methionine rich, acidic, hydrophobic • Highly conserved primary structure • Helical protein	25	• Neurotransmission regulation • SV fusion • SNAP receptor activity • Calcium binding	SCZ, BD, ADHD, ASD, AD, Neuroticism	(Barr et al., 2000; Brinkmalm et al., 2014; Etain et al., 2010; Guerini et al., 2011; Kim et al., 2017b; Shen et al., 2014; Yang et al., 2017)
VAMP	• SV-associated membrane protein • Conserved across species • Exists in dimeric form	12.9	• SV targeting and transfer • SNAP receptor binding • Syntaxin binding	SCZ, BD, ADHD, AD, Multiple sclerosis	(Bourassa et al., 2012; Kenar et al., 2014; Morris et al., 2018; Ramos-Miguel et al., 2015; Sevlever et al., 2015)
Syntaxin	• Membrane integrated Q-SNARE protein • Contains a single C-terminal TM domain, a cytoplasmic domain with 265 residues	33	• Neurotransmitter exocytosis • ATP-dependent protein binding	Williams-Beuren syndrome, SCZ ASD, ADHD	(Cartier et al., 2015; Castillo et al., 2010; Kenar et al., 2014; Osborne et al., 1997)
Synaptotagmin	• An integral membrane protein. • Multidomain protein (N-terminal TM region, a variable linker, and two C-terminal C2 domains - C2A and C2B)	47.5	• Early SV docking • Ca^{2+}-evoked SV fusion	Dyskinetic z movement disorder, AD, PD, BD	(Baker et al., 2015; Brinkmalm et al., 2016; Moghaddam and Arabi, 2018; Shao et al., 2016)

Table 1b
interactors of SNARE complex proteins, their properties and associated diseases.

Proteins	Structural feature/Properties	Mol.wt (kDa)	Molecular function	Diseases	Reference
NSF	Features an amino-terminal domain(N) and two domains (D1 and D2) for ATP binding.	82.5	SV fusion, SNARE complex disassembly	SCZ, BD, AD	(Gray et al., 2006; Ikin et al., 2007; Lenzen et al., 1998)
PRR2	Features transcription factor region including a GARP DNA recognizing domain, a proline-rich region, and a GCT box. Proline-rich region acts as transactivation domain.	34.9	Syntaxin binding	Epilepsy, Kinesigenic dyskinesia	(Heron and Dibbens, 2013; Li et al., 2015)
NRG3	Comprises of an extracellular domain with an epidermal growth factor motif, a TM domain and a cytoplasmic domain. EGF binds the extracellular domain of ErbB4.	77.9	Tyrosine phosphorylation and receptor activation	SCZ, BD	Zhang et al. (1997)
Munc-13	Complex domain assembly with C1 carboxyl domain (homologous to PKC) and C2 domains (provides Ca^{2+} and phospholipid binding site)	180	Neurotransmitter release, Refilling of SV pool, Rab GTPase binding	SCZ, BD, HD, PD	(Brose et al., 2000; GUERRERO et al., 2012; Torres et al., 2017)
Munc-18	Contains multiple kinase recognition sites and specific to syntaxin binding	67	Exocytosis of neurons and neuroendocrine cells	Epileptic encephalopathy, early infantile,4 (EIEE4)	Saitsu et al. (2008)

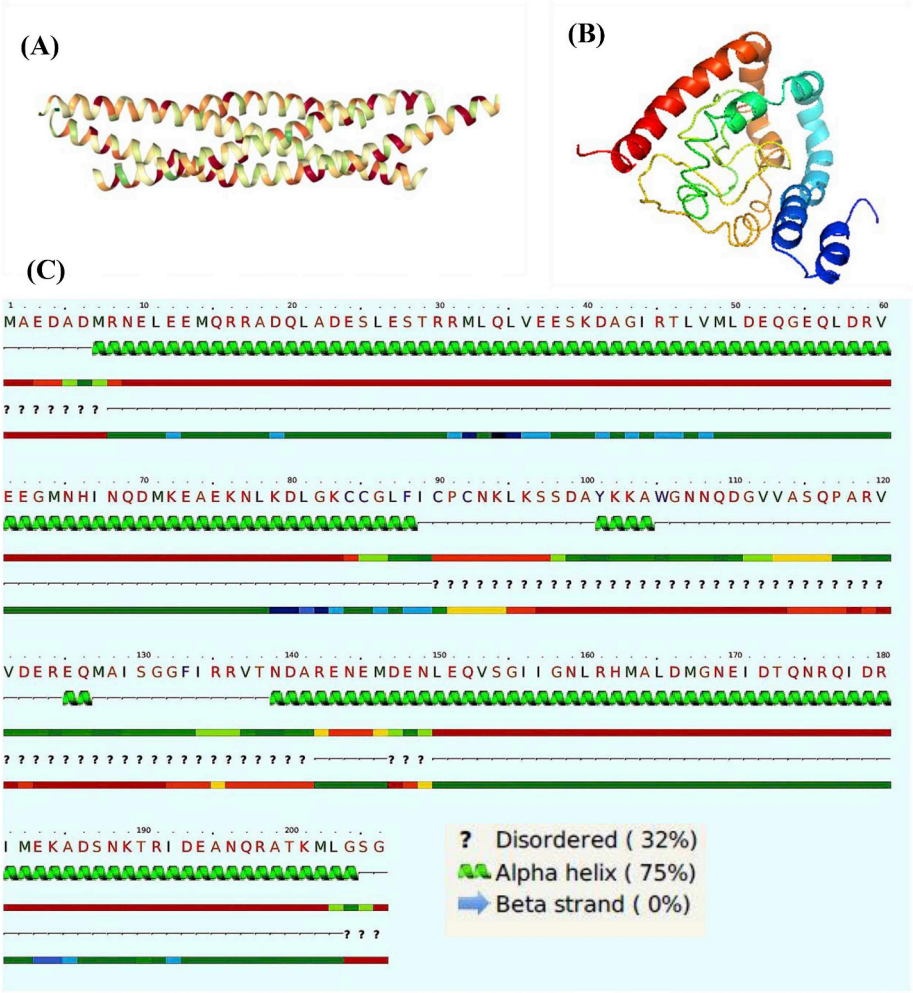

Fig. 2. Three-dimensional structure of the truncated SNARE complex (PDB: 3RK2) (A); 3D structure of SNAP25 alone generated by homology modelling (B); Prediction of the disordered and secondary structure of SNAP25 (C).

structure of SNAP25 using Phyre2 software, which is found to be 32% disordered and 75% helical. Hence, the computational studies performed here presented SNAP25 as an intrinsically disordered and aggregation prone protein.

Furthermore, the cysteine-rich domain is of particular importance, because it is found to regulate the intracellular distribution of the protein besides plasma membrane affixing (Greaves and Chamberlain, 2011). SNAP25 undergoes several post-translational modifications, out of which, the addition of palmitic acid (palmitoylation) to its cysteine-rich region (residues 84–92) results in the anchoring of SNAP25 at the pre-synaptic PM (Veit et al., 1996). The Cys90 residue has been recently found to be a target of S-guanylation (the addition of 8-nitro-cGMP to thiol group). This was found to influence the assembly/disassembly of SNARE complex by attenuating the interaction between complexin and SNARE complex (Kishimoto et al., 2017). SNAP25 also undergoes phosphorylation by the enzyme, Protein Kinase C (PKC), which modulates the Voltage-Gated Calcium Channels (VGCCs). This process accelerated the exocytosis of neurotransmitters by recruiting secretory vesicles to the presynaptic PM (Nagy et al., 2002; Pozzi et al., 2008). A recent report by Katayama et al. on the phosphorylation of SNAP25 at the ser 187 residue suggested that this event is crucial in regulating neurotransmitter release and short-term plasticity (Katayama et al., 2017). The residue, thr138, is yet another target of phosphorylation/dephosphorylation by RhoA-activated Kinase (ROK) and Myosin Phosphatase (MP), which have been reported to modulate the interaction between SNAP25 and syntaxin (Horváth et al., 2017). Additionally, the tyrosine residues of SNAP25 and Munc18 (interactor of SNARE complex) have been found to undergo 3-nitrosylation induced by peroxynitrite. The event influenced the intermolecular interaction between SNAP25 and Munc18 (Di Stasi et al., 2002). Therefore, it is realized that SNAP25 undergoes several structural modifications before and after attaining its native helical structure for performing multifaceted tasks. With this perspective, the following sections depict the functional role of SNAP25 in the presynaptic and postsynaptic compartments.

2.2. Function of SNAP25

2.2.1. Role in presynaptic events

SNAP25 interacts with a number of synaptic proteins and forms several complexes which cause conformational changes in SNARE assembly and presynaptic PM dynamics. It has been already ascertained that SNARE complex functions in an intricate network of protein-protein interactions. A recent study demonstrated that the interaction of SNAP25 with Rabphillin-3A which is endowed with a C2 domain (a common motif with synaptotagmin to sense Ca^{2+}) promoted presynaptic PM bending. Rabphillin-3A was found to interact with SNAP25 (at the same site as synaptotagmin) and also with Phosphatidyl-Inositol-4,5-bis-Phosphate (PIP_2) to attain a specific conformation. The resultant complex was capable of interacting with the whole SNARE organization and influence the presynaptic events significantly (Ferrer-Orta et al., 2017). Gβγ (a $G_{i/o}$-coupled G protein-coupled receptor) has also emerged as a competitor of synaptotagmin for binding with SNAP25b

and was found to inhibit Ca^{2+}-triggered exocytosis in a concentration-dependent manner (Zurawski et al., 2017). With this finding, it can be concluded that Gβγ-SNARE interaction is undesirable. Also, SNARE complex appears to be a highly complicated network as another study demonstrated that eliminating Gβγ-SNARE interaction resulted in SNARE dysfunction (Zurawski et al., 2018). It indicated that SNARE-Gβγ interaction is also an essential component of the neurotransmission process. We can therefore speculate that the aforementioned interaction can be fitted into the established competitive and substrate inhibition models. This point of view to analyze SNARE complex interaction with other interactors might shed new insights, and a mathematical model of SNARE complex interaction might arise as well.

Mutation studies in SNAP25 and its implication in the presynaptic events was reported by Verderia et al., where SNAP25 silencing in the glutamatergic neurons resulted in an increased presynaptic Ca^{2+} level. Furthermore, the crucial role of residues 180–197 in the modulation of calcium dynamics was also recognized (Verderio et al., 2004). Previous reports suggested that the C-terminus of SNAP25 interacts with synaptotagmin (Syt1) which is essential for Ca^{2+} dependent binding of Syt1 to SNARE Complex (Gerona et al., 2000). Additionally, C-terminal zipping of SNAP25 was also found to trigger fusion pore opening and bringing about conformational changes in SNARE complex (Fang et al., 2008). Recently, a novel missense SNAP25b mutation (c.176G > C, p. Arg59Pro) has been identified in two siblings affected by cerebral ataxia leading to seizures. Interestingly, the mutation was inherited from the father who remained unaffected (Fukuda et al., 2018). It was an indication that the manifestation of an aberrant SNARE structure leading to neurological debility not only depends upon the alteration in the gene but on the protein folding mechanism. This might be a reason for which the same mutation caused different expression in the father and offsprings. Two SNAP25b mutations, I67T and 167N, revealed a weakening of the zipping of SNAP25 C-terminus, which has been previously mentioned to take part in triggering fusion pore opening. However, the mutations did not affect N-terminal assembly but destabilized SNARE complex by impairing the folding of t-SNARE (i.e. SNAP25b) (Rebane et al., 2017). Recent researches are turning towards linking the misfolding of SNARE proteins with the dysfunction of SNARE complex in neurological disorders.

2.2.2. Role in postsynaptic events

SNAP25 is an emerging role-player in the postsynaptic compartments as well, with significant involvement in the regulation of spine morphogenesis. Primarily it is attributed to the ability of SNAP25 to bind with presynaptic PM and an adaptor protein, p140Cap. The latter plays a key role in regulating the formation of spine and actin cytoskeleton. Tomasoni et al. reported that SNAP25 allowed the spine-forming molecular apparatus to be organized by the recruitment and stabilization of p140Cap (Chin et al., 2000; Tomasoni et al., 2013). The aberrant expression of SNAP25 has been linked to the disorganization of the postsynaptic events. At low levels of SNAP25, the phenotypic expression of dendritic spines was found to be immature and consistently less functional. However, its overexpression led to an elevation in the level of mature Postsynaptic Density Protein-95 (PSD-95). Possibly, SNAP25 influences the postsynaptic events through its interaction with PSD-95, which appeared to regulate the molecular organization of postsynaptic density (Chen et al., 2011; Repetto et al., 2014; Tomasoni et al., 2013; Yang et al., 2015). Another report on similar lines showed that the clustering of PSD-95 is indeed controlled by the cellular level of SNAP25 through forming a complex with p140Cap and PSD-95. Acute downregulation of SNAP25 in the CA1 hippocampal neurons of heterozygous mice exhibited distorted PSD-95 dynamics and reduced density of dendritic spines (Fossati et al., 2015). It is to be understood that SNAP25 regulates postsynaptic events through its interactions with the proteins, PSD-95 and p140Cap. Therefore, exploration of the role of these proteins is a background investigation of SNAP25 interactions in postsynaptic compartment. Contextually, it has been recently demonstrated that the dendritic spines formed in the p140Cap knockout mice were immature and filopodia-like. The aberration was found to manifest in cognitive deficits, long-term depression (LTD) and long-term potentiation (LTP).

SNAP25 is not only found to regulate spine morphogenesis but various reports have also confirmed its participation in axonal growth during the late elongation stages. It has been suggested that area-specific level of SNAP25 in the adult brain contributes to nerve terminal plasticity (Osen-Sand et al., 1993). SNAP25 also influences the internalization of a separate class of postsynaptic receptors, the kainate receptors, and modulates postsynaptic plasticity (Selak et al., 2009). Therefore, it is conclusive that the expression, folding and interactions of SNAP25 are quintessential in normal brain physiology and anomaly in any of these processes has serious neuropathological implications. The following sections enlist the aberration of SNAP25 expression, organization and other interactions with common links across a diverse spectrum of synaptopathies and neuropathies.

3. SNAP25, a common neuropathological hallmark

The aberration in site-specific SNAP25 expression is a hallmark in several neurological disorders and has been confirmed in SCZ (Thompson et al., 1998), BD (Etain et al., 2010), ADHD (Barr et al., 2000), Major Depressive Disorder (MDD) (Kim et al., 2007), and ASD etc. (Guerini et al., 2011). Interestingly, some symptoms like memory dysfunction and dysregulation of circadian rhythm, which are manifested in neurological disorders or synaptopathies are also shared by neurodegenerative diseases or the proteopathies (Noda et al., 2003; Wulff et al., 2010). The latter is associated to misfolding and aggregation of proteins (Das et al., 2017; Kabuta et al., 2006; Karmakar, 2017; Pandey et al., 2012; Sakurai et al., 2008). In that light, SNAP25 can be viewed as a nexus between synaptopathies and proteopathies. The presence of multimeric SNAP25 aggregates in neurological disorders (Ramos-Miguel et al., 2017) and the aberrant expression in a number of neurodegenerative diseases (Brinkmalm et al., 2014; Greber et al., 1999; Yun et al., 2013) is suggestive of the same.

3.1. Implication in neuropsychological disorders

The levels of axon-associated proteins, namely synaptotagmin, β-tubulin, kinesin-1, and SNAP25 were found to be expressed in significantly reduced levels in the prefrontal white matter of BD sufferers (Shao et al., 2016). Actually, axonal density and axonal function have been found to be disrupted in BD sufferers. Another study elucidated the association of a SNAP25 promoter variant, *rs6039769,* to the early commencement of BD with a higher level of gene expression in the human prefrontal cortex. The promoter variant was also found to have a linkage to SCZ alongside exhibiting an aberrant ratio of snap25a/snap25b (Houenou et al., 2017). A recent report demonstrated the expression of SCZ-like phenotypes in the SNAP25 conditional knockout (cKO) mice. The extracellular glutamate level was found to be elevated significantly in the cerebral cortex of dissected brains along with elevated levels of syntaxin and VAMP in the cell membrane. This glutamatergic pathogenesis of SCZ in the presynaptic and postsynaptic compartments was found to be associated with aberrant SNAP25 level (Yang et al., 2017). A study associated the clinical phenotype of SCZ, cognitive dysmetria, with the alteration of SNAP25 expression (Mukaetova-Ladinska et al., 2002). Fig. 3(B) represents the decrease in the levels of SNAP25 in the schizophrenic cerebellum as compared to the normal (control of the study shown in Fig. 3(A)). Furthermore, the postsynaptic levels of PSD-95 and *N*-Methyl-D-aspartic acid (NMDA) receptors (important interactors of SNAP25) were significantly reduced in the prefrontal cortex of SCZ sufferers (Catts et al., 2015).

The effect of prenatal stress (PS) on the psychophysiology of offspring has been well observed from a long time. Illuminating the molecular mechanism of depressive behaviour induced by PS on rat

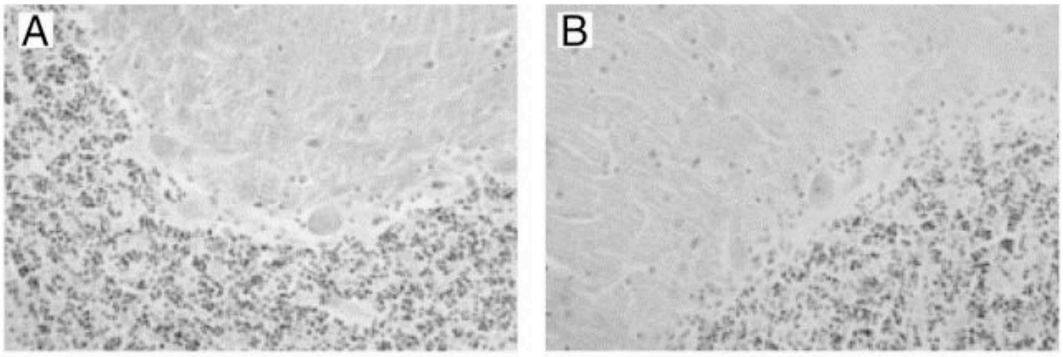

Fig. 3. SNAP25 distribution in the normal cerebellum (A); Reduction of SNAP25 level in the schizophrenic cerebellum (B). Adapted with permission from (Mukaetova-Ladinska et al., 2002).

offspring, Cao et al. demonstrated that the expressions of SNAP25, syntaxin, and VAMP increases in PS leading to enhanced SNARE complex formation. Furthermore, the expression of vGluT1 (Vesicular Glutamate Transporter 1), a glutamate/proton exchanger, which regulates crucial activities in the glutamatergic synapse, was also elevated. These aberrant expressions affirmed the notion that vesicular glutamate transporters and subsequent glutamate release play key roles in the depressive behaviour of rat offspring (Hewett et al., 2016; Martineau et al., 2017; Jun Cao et al., 2018). Confirmation of this trend in humans will be intriguing and requires further research.

The contribution of SNAP25 aberration in ASD has received considerable attention. The cognitive deficits in ASD patients have been attributed to the polymorphism of SNAP25 gene. The presence of the allele, rs363050(G), was supposed to be responsible for the reduced expression of SNAP25, which led to autistic symptoms along with schizophrenic and epileptic symptoms in a mice model (Braida et al., 2016). A recent study on Iranian population further revealed the drastic consequence of SNAP25 Single Nucleotide Polymorphisms (SNPs) in brain physiopathology leading to psychiatric disorders. A robust association of the SNAP25 allele, rs3746544 SNP, to the autistic behaviour in ASD patients has been reported in the aforementioned study. SNAP25 was presented as a susceptibility genetic factor involved in the development of ASD (reza Safari et al., 2017). Another study performed on a population of Korean children who were suffering from ADHD revealed that SNAP25 polymorphism is associated to the inattention phenotype (Kim et al., 2017a; Liu et al., 2017). These findings indicated the possible role of SNAP25 polymorphism as a common hallmark of psychiatric disorders. It can be hypothesized that the polymorphism of SNAP25 gene translates into conformational variants which results in altered protein-protein interactions. These conformational variants of SNAP25 presumably interacts with other SNARE proteins either too strongly or too weakly resulting in extremely unstable or extremely stable SNARE complexes. Weak interactions of SNARE proteins result in a destabilized SNARE assembly, whereas, extremely strong interactions anomalously increase its stability which becomes resistant to disassembly. Both of the events presumably introduce aberration in the structural organization of SNARE complex altering its functional attributes. A list of SNAP25 polymorphisms and their association with several other neurological disorders are summarized in Table 2.

The other fundamental SNARE proteins, namely, syntaxin and VAMP, are also associated with neurological disorders. These proteins share no less responsibility than SNAP25 in destabilizing SNARE complex and disrupting neuronal signaling. Syntaxin1B (a syntaxin isoform) encoded by the Stx1B gene has been associated to epilepsy and febrile seizures by affecting the glutamatergic and GABAergic neurons. Introducing a mutation in the gene was found to form undersized synaptic vesicles and increase motor cortex excitability in febrile seizures and epilepsy (Schubert et al., 2014; Stefanou et al., 2017). A post-translational modification of syntaxin, namely, serine 14 phosphorylation and C-terminal sumoylation, was found to lower the protein-protein interaction between SNARE components resulting in a misassembled SNARE complex (Cartier et al., 2015; Craig et al., 2015). Coming to the role of VAMP or Sb, Koo et al. demonstrated that a large vesicular VAMP pool is essential in maintaining the efficiency of neurotransmission and reformation of SV. VAMP-specific adaptor protein AP180 was found to preserve the vesicular pool of VAMP/Sb (Koo et al., 2015). Ap180 has also been linked to established “synaptopathies” like ASD and BD (Ben-David and Shifman, 2012; Goes et al., 2012). A VAMP mutation, homozygous c.340delA frameshift, has been recently found to be associated with the congenital myasthenic syndrome, a neuromuscular disease (Shen et al., 2017). Therefore, to briefly summarize the involvement of syntaxin and VAMP, it can be stated that the core structure of a functional SNARE complex is dependent on the interactions of these proteins to SNAP25. Any defect arising in any of the four helices of SNARE complex can modify its structure and function.

3.2. Implication in neurodegenerative diseases

Neurodegeneration is accompanied by an anomaly in synaptic transmission, and it will be without surprise if SNAP25 which is a vital component of the presynaptic and postsynaptic compartment emerge as a role player. SNAP25 as a novel biomarker of neurodegeneration was first presented by Brinkmalm et al. reporting elevated levels of the protein in cerebrospinal fluid at the early onset of AD. Emphasis on the synaptic biomarkers like SNAP25 was laid for the development of diagnosis, progression and therapeutic standing of neurodegenerative diseases (Brinkmalm et al., 2014). On similar lines, increased levels of SNAP25 have been found to be mirrored by the changes occurring in Amyloid Precursor Protein (APP) and Amyloid-β (Aβ) levels in AD (Bailey and Lahiri, 2006). Therefore, a possible link between neurodegenerative pathways with synaptic defects can be very well speculated. A recent study determined the aggregation propensity of SNAP25 employing SDS-PAGE, which revealed that the protein is capable of self-assembling to ~480 kDa aggregates. Furthermore, the hippocampal sections of an AD patient revealed the presence of similar SNAP25 aggregates (Ramos-Miguel et al., 2018). Recently, elevated baseline levels of SNAP25 (along with other synaptic proteins) has been presented as an indicator of amyloid-positivity and clinical status. The level of these neuronal injury markers has been observed to undergo longitudinal decrease at the late onset of AD (Sutphen et al., 2018). A report outlined a link between diabetes and neurodegeneration in the context of SNAP25- Caveolin 1 interaction leading to disruption in the synaptic events (Braun and Madison, 2000; Cohen et al., 2003; Greaves et al., 2009; Magga et al., 2002). In addition, amyloid fibrils interfere in SNARE fusion process by disrupting the recycling and assembling of SNARE constituent proteins (Garcia-Reitböck et al., 2010; Shen, 2010). The Aβ42 peptide chain has been suggested to control neurotransmitter release possibly by perturbing the formation of SNARE complex

Table 2
SNAP25 polymorphism and their association with several neurological disorders.

SNP	Locus	Pathological symptom(s)	mRNA/protein aberration	Reference
rs6039769	Promoter	BD episodes	SNAP-25 level increases	(Etain et al., 2010)
rs363039	Intron 1	IQ changes in some patients, hyperactivity in autistic association impairment	Transcription binding site	Braida et al. (2016)
rs353016		Variation in IQ		Gosso et al. (2006)
rs6108461	Intron 3	ADHD—regulation of attention and inhibition	SNAP-25 level Decreases	(Hawi et al., 2013{26)
rs362990	Intron 4	ADHD with hyperactivity phenotype	SNAP-25 level Decreases	Hawi et al. (2013)
rs3746544	3′UTR	Hyperactivity,	One copy of the SNAP-25 gene is	Kim et al. (2017a)
rs1051312		Impulsivity	Mutated	(Ye et al., 2016)
		May increase the	N/D	
		Level of ADHD		

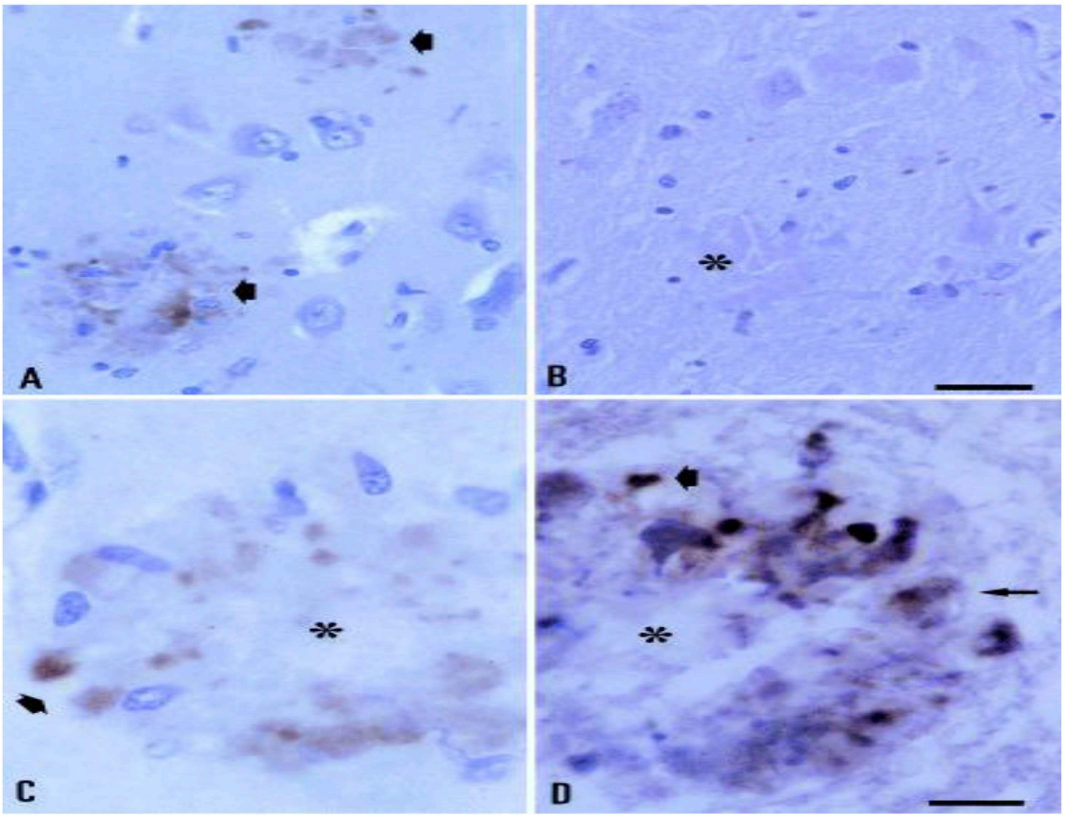

Fig. 4. The immunoreactivity of Dpl which takes place in aberrant neurites of AD senile plaques (highlighted with arrows) (A, C, D); Dpl immunoreaction was abolished by its co-incubation with an antigenic peptide (sc-16862P) prior to immunohistochemistry (B); Co-localization (highlighted with long arrows) of Dpl (brown precipitate) and SNAP25 (dark blue precipitate) in dystrophic neurites (C and D). Asterisks indicate the amyloid cores of neuritic plaques. Bars: (A,B) 25 μm; (C,D) 10 μm. Adapted with permission from (Ferrer et al., 2004). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

through its competitive affinity with synaptophysin. This particular event has been found to implicate in the pathogenesis of AD (Russell et al., 2012). Also, a decreased level of a SNARE interactor, Rabphilin 3A, has been found to be associated with Aβ burden in AD (Tan et al., 2014). In vascular dementia (a related form of dementia in AD) the temporal proteins including SNAP25 was found to be differentially expressed and de-amidated causing synaptic decay (Gallart-Palau et al., 2015). In light of that, Fig. 4 shows the findings of Ferrer et al., which demonstrated the interaction of SNAP25 and Doppel (Dpl), a prion-like glycosylphosphatidylinositol – anchored protein. Both of the proteins were found to be associated with the dystrophic neurites of senile plaques in AD (Ferrer et al., 2004). Thus, it can be very well observed that a structural aberration of SNARE complex affects several brain activities and manifests in cognitive impairment, dementia, and seizures, etc.

Coming to the role of SNAP25 in PD, a recent study reported the depletion of SNAP25 along with syntaxin and munc-18 resulting in massive cell death of cultured neurons even before the commencement of synaptic events. A depletion of SNAP25 level along with syntaxin, and munc-18 also manifested into abnormalities in golgi complex. Therefore, the core SNARE proteins can indeed be viewed as modulators of α-synuclein neuropathy (Santos et al., 2017). Moreover, a similar distribution profile of the vesicle-associated α-synuclein and SNAP25 was found in familial PD. This was indicative of the involvement of SNAP25 in the heredity of PD (Jensen et al., 1998). A mutation in the Leucine-Rich Repeat Kinase 2 (*LRRK2*) gene, which is causative of the autosomal-dominant familial PD, has been found to phosphorylate snapin (a SNARE interactor) and inhibit its interaction with SNAP25. Consequently, it was observed that SNARE assembly was affected and the number of releasable vesicles had declined steeply (Yun

et al., 2013). LRRK2 has also been revealed to phosphorylate NSF, which increases its ATPase activity and thereby, SNARE complex disassembly is upregulated (Belluzzi et al., 2016). Also, the aforesaid gene has been found to regulate clathrin-mediated endocytosis of SVs and regulate neurotransmission (Arranz et al., 2014). Thus, the disruption of neurotransmission and cognitive deficits in PD can be linked to SNARE complex components especially with SNAP25.

An association of the activity loss of SNAP25 and Rabphilin 3A with some of the symptoms of Huntington's Disease (HD) was revealed in a study by Smith et al. The down-regulation of these proteins was found to affect neurotransmitter release in HD cortical neurons (Smith et al., 2007). Intriguingly, a study demonstrated the interaction of SNAP25 and the Hungtington's protein (Htt) through co-immunoprecipitation in mouse neurons and thereby, SNAP25 was reported as a genetic modifier of HD neurodegeneration (Kaltenbach et al., 2007). Recent studies have pointed towards the involvement of SNAP25 and Syntaxin1B in Amyotrophic Lateral Sclerosis (ALS) or the motor neurone disease. Strong deregulation of the pair was observed both at the mRNA and protein levels causing impaired synaptic function. The SNAP25 reduction has been anticipated as the possible reason for glutamate excitotoxicity and Ca^{2+} elevation in the dysfunction of glutamatergic synapse (D'erchia et al., 2017). The alteration in the levels of SNAP25 in ALS shared similar patterns as exhibited in AD, which suggests that different proteopathies might share SNAP25 as a common marker (Ikemoto et al., 2002). Hence, increasing number of findings on the common alteration of SNAP25 expression and structural aberration in different synaptopathies and proteopathies provokes a new perspective to unify their pathogeneses.

4. Discussion

The goal of this review was to find a nexus between synaptopathies and proteopathies in the context of a common synaptic marker, SNAP25. The aggregation prone nature of SNAP25, according to computational modelling, is intrinsic and shares similar patterns with well-known amyloidogenic proteins. The aberration of SNAP25 structure plays a crucial role in destabilizing its supramolecular organization in SNARE complex and seriously implicates neural signaling. The structural and functional attributes of the protein is governed by some of its most important post-translational modifications. Perhaps, an anomaly in the post-translational modification alters the functional structure of SNAP25 and increases its amyloidogenic propensity. Various reports in this direction has highlighted that SNARE complex assembly is a fine model for protein folding and protein interactions. The homotetrameric aggregates of SNAP25, which have been reported in the autopsied orbitofrontal cortex of SCZ and MDD sufferers, validate the amyloidogenic nature of SNAP25. The misfolded aggregates identified by Ramos-Miguel et al. in the above study were found to be ~50 (homodimeric), ~75 (homotrimeric), and ~110 (homotetrameric) kDa. The tetrameric aggregates were found to be a 7.2 fold greater in people with SCZ than the control group. It was hypothesized that presynaptic overstimulation resulted in biochemical stress on SNARE complex leading to the faulty organization through SNAP25 misfolding (Ramos-Miguel et al., 2017). Further, higher order aggregates of SNAP25 (~480 kDa) were also detected, and it was observed that SNAP25 can self-aggregate (Ramos-Miguel et al., 2018). As already mentioned above, the helical protein is an intrinsically disordered protein and might be amyloidogenic as well. The amyloidogenicity of a protein is governed by its intrinsic amino acid sequences. Therefore, we have attempted to locate the amyloidogenic regions of SNAP25 using Foldamyloid software (Garbuzynskiy et al., 2009). The results of this computational findings are marked bold in the following FASTA sequence:

MAEDADMRNELEEMQRRADQLADESLESTR**RMLQL**VEESKDAGI**RTLVML**DEQGEQLDRVEEGMNHINQDMKEAEKNLKDLGK**CCGLFIC**PCNKLKSSDAYKKAWGNNQDGVVASQPARVVDEREQMAISGGFIRRVTNDARENEMDENLEQVSGIIGNL**RHMAL**DMGNEIDTQNRQIDRIMEKADSNKTRIDEANQRATKMLGSG

Foldamyloid identified four amyloidogenic regions which were (i) RMLQL (31–35), (ii) RTLVML (45–50), (iii) CGLFIC (85–90) and (iv) RHMAL (161–165). Out of the four regions, it can be noticed that the third region, CGLFIC, is located in the cysteine-rich domain of SNAP25, where it is palmitoylated leading to membrane anchoring. It can be speculated in this direction that an aberration at this region might result in the non-adherence of SNAP25 to the PM. A possible link between hydrophobicity, protein adsorption and protein aggregation at amphiphilic self-assembled monolayers (SAMs) was demonstrated by Pandey et al. (Pandey et al., 2012, 2013; Pandey and Pattanayek, 2011), which can possibly explain the aggregation of this system. Surface adsorption of a protein brings about changes in its secondary structure (Hasan et al., 2018; Pandey, 2012; Pandey and Pattanayek, 2011, 2013a, b), which in turn regulates its functionality. A recent report by the our research group elaborated the mechanistic insights of BSA fibrillation dependent on the interaction of Cu^{2+} at several stoichiometric ratios (Singh et al., 2017). In this direction, the cysteine-rich domain of SNAP25 is very similar to many of the metalloproteases like metallothionein and liver alcohol dehydrogenase, which is suggestive that SNAP25 might also co-ordinate with metal ions (Berg, 1986; Oyler et al., 1989). Possibly, the decreased levels of SNAP25 in the zinc-transporter 3 knock-out mice is related to the binding of SNAP25 with zinc but further extensive research is required to establish the notion. Interestingly, it has been reported decades ago that synaptotagmin undergoes oligomerization in a Ca^{2+} dependent manner (Damer and Creutz, 1996). Along these lines, SNAP25 aggregation might also be responsible for its dynamic interaction with metal ions at the cysteine-rich region, which is prone to aggregation. Additionally, the Cys90 residue which was found to regulate SNARE complex formation through S-guanylation also lies in the amyloidogenic region, **CGLFIC**. Perhaps, the post translational modifications at this region greatly influence SNAP25 structure and function. A fault in the post-translational processing of SNAP25 can be anticipated to reflect in the folding patterns of SNAP25. It is also known that the products of the proteolytic cleavage of APP vary in their amyloidogenic propensity with Aβ42 being the most amyloidogenic one. In order to explore whether a proteolytic product of SNAP25 can influence SNAP25 aggregation, a section of SNAP25 from residues (71–103) containing the cysteine-rich amyloidogenic domain was separately modelled using Phyre2. The predicted secondary structure of the segment showed β-sheet formation at the cysteine-rich domain (shown in Fig. 5), which otherwise was not predicted when the full sequence was modelled (shown in Fig. 2). This is speculative of the sensitivity of the cysteine rich region to be a nucleating site for SNAP25 aggregation.

Coming to the role of protein-protein interaction, Ramos-Miguel et al. reported that abnormal SNARE protein interactions manifest in the dysfunction of the complex in SCZ. In the study the core constituents of SNARE complex (i.e. SNAP25, syntaxin, VAMP) were found to anomalously interact like Munc-18, complexin, and synaptotagmin. This resulted in the formation of abnormal heteromers of SNAP25-VAMP with overexpression of 150 kDa heterotrimers and low expression of 70 kDa heterodimers. Furthermore, significant upregulation of 200 kDa SNARE-complexin pentameric complex was observed along with downregulation of complexin containing 550 kDa aggregates. Abnormal increase in the binding of Munc-18 and complexin manifested in the overexpressiion of SNARE complex (Ramos-Miguel et al., 2015). An irregularity in the interaction of SNAP25 and synaptotagmin in SCZ was also reported elsewhere suggesting that altered protein-protein interactions in the synaptic events manifest in erratic brain physiology through misfolded SNARE complexes (Barakauskas et al., 2010; He et al., 2017). The varied interactions of the synaptic proteins seem to chaperone the folding of SNARE complex and portray it to be a chaperone-mediated folding system of extremely complex nature.

The interactions of SNARE complex proteins have been mostly

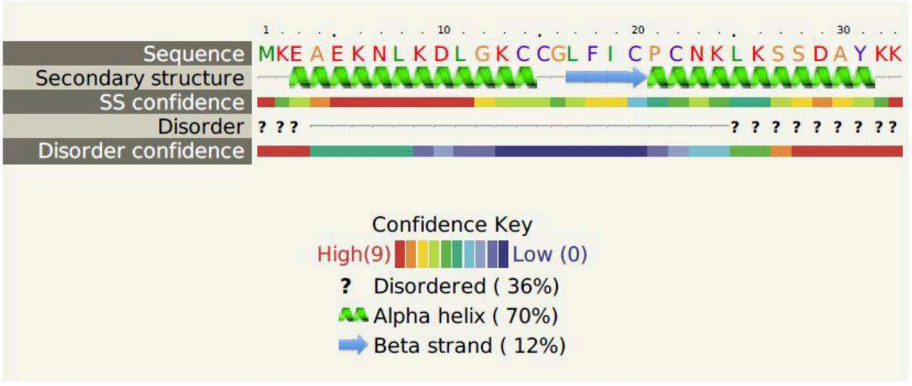

Fig. 5. Prediction of the secondary structure of SNAP25 segment from residues 71–103 displaying β-sheet formation at the cysteine-rich amyloidogenic domain.

found to be disrupted with faulty post-translational modifications. Out of which, phosphorylation of serine residues of SNAP25 and syntaxin has been found to contribute to the maximum effect. In a report, deficits of phosphoserine in syntaxin reduced binding affinity between SNAP25 and Munc-18, resulting in decreased formation of SNARE complex in SCZ (Castillo et al., 2010). Conversely, dephosphorylation altered SNARE complex size from 150 kDa to 200 kDa, which was found to be a result of increased binding of complexin, Munc-18, and synaptotagmin to SNARE complex (Ramos-Miguel et al., 2015). Presumably, anomalous elevation in the interactions of synaptic proteins leads to an aberrant increase in the enthalpy of the system. This halts the disassembly of SNARE complex, recycling of SNARE proteins and, subsequently leads to cellular accumulation.

Several chaperones have been reported which assist the folding of SNARE complex into its functional structure. A chaperone complex of Hsc70, SGT (Small Glutamine-rich Tetratricopeptide repeat protein) and CSPα (cysteine-String Protein-α) has been reported to bind to the monomers of SNAP25 and prevent its aggregation. The deletion of CSPα gene has been found to produce aberrant conformers of SNAP25 subjected to ubiquitination, revealing that there are unique protein folding and quality control mechanisms in the presynaptic compartment (Sharma et al., 2011). One of the chaperones of SNARE complex has been found to be α-Synuclein, which is a well-known pathological hallmark of PD accompanied by cognitive deficits and dementia. A study reported that α-Synuclein promotes SNARE complex formation through its multimerization after membrane binding (Burré et al., 2014). Furthermore, α-Synuclein has been also found to promote SNARE complex-mediated SV docking and membrane fusion by interacting with VAMP (Hawk et al., 2018). However, its overexpression was observed to redistribute and misregulate the constituents of SNARE complex. It appeared that the chaperoning effect of α-Synuclein was dependent on the optimum expression of the protein (Bridi and Hirth, 2018). Lower interactions of SNAP25/syntaxin and complexin-2 (a complexin isoform) were linked to dementia and cognitive impairment in PD. The above interaction was coupled with the overexpression of α-Synuclein, which affected the dopaminergic neurons (Honer et al., 2012; Pavia-Collado et al., 2018). Therefore, it appears that the pathogenesis of the synaptopathies and proteopathies share common aberration in protein-protein interactions, faulty post-translational modification and structural malformation. In summary, the proper folding of SNARE complex is the prime essential factor in maintaining healthy physiology of the brain. Indeed, a disturbed or depressed mind is a manifestation of the physiological dysfunctions as prefigured decades ago by Anukulchandra (Chakravarty, 1965). SNARE physiology has a prime involvement in the overall psycho-physical health and SNAP25 is presented as a neuropathological hall mark for therapeutic and diagnostic inventions.

5. Conclusions

Based on the evolution of SNARE research till date, it can be comprehended that the prime essentiality in maintaining healthy physiology of the brain is the proper functioning of SNARE complex. The nexus between protein interactions of this complex, protein folding mechanisms and stoichiometric metal ion interactions to neurophysiology are evident. Although, the fundamental research on the nature of SNARE complex is profuse, yet, there appears to be a lack in the development of diagnosis and therapy for the associated synaptopathies. This review presents SNARE complex component, SNAP25, as a potential biomarker and therapeutic target for a number of neuropathological conditions. SNAP25 is a small 25 kDa helical protein, which is the prime contributor in the SNARE complex assembly. It is shown that this protein is found to have aggregation prone (amyloidogenic) regions. Numerous studies have reported the altered complex assembly in case of neurological disorders. The aberrant structures of SNAP25 are resulted due to any changes in those amyloidogenic regions and are primarily recognized for the alteration in the complex assembly. Furthermore, aggregation of this protein is established to cause a diverse synaptopathies and proteopathies. The need of the hour is extensive research focussing on the physiological aspects of the psychiatric disorders to detect the onset, progress and further neuronal deterioration. It is quite unfortunate that most observations on the dysfunction of SNARE complex were done on the autopsied brains. Therefore, a greater focus on SNARE complex-associated neuropsychology is urgent, alongside the need of acceptance and positive representation of the patients in the society. At a more humane level, support and physical presence of family and friends, and awareness of these disorders might save many lives from further deterioration. The sufferers need to be understood in a way that these conditions are much more physiological than they appear, to which there is little to select. Hopefully, this review would present SNARE associated brain physiology towards further research focussing on diagnosis and therapeutics with a more humanistic motivation.

Acknowledgement

The authors wouldlike to thank the Department of Science and Technology, Government of India for financial assistance (Sanction nos: DST/INSPIRE/04/2014/002020, ECR/2016/001027).

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