Published in final edited form as:

Ann N Y Acad Sci. 2009 January ; 1152: 93–99. doi:10.1111/j.1749-6632.2008.03995.x.

SNAP-25 IN NEUROPSYCHIATRIC DISORDERS

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Abstract

SNAP-25 is plasma membrane protein which, together with syntaxin and the synaptic vesicle protein VAMP/synaptobrevin, forms the SNARE docking complex for regulated exocytosis. SNAP-25 also modulates different voltage-gated calcium channels, representing therefore a multifunctional protein that plays essential roles in neurotransmitter release at different steps. Recent genetic studies of human populations and of some mouse models implicate that alterations in SNAP-25 gene structure, expression and/or function may contribute directly to these distinct neuropsychiatric and neurological disorders.

Keywords

SNAP-25; schizophrenia; epilepsy; ADHD; calcium channels

SNAP-25: A MULTIFUNCTIONAL PROTEIN REGULATING SYNAPTIC TRANSMISSION

SNAP-25 (synaptosomal-associated protein of 25 kDa) is a SNARE protein that participates in the regulation of synaptic vesicle exocytosis. It is a membrane bound protein anchored to the membranes of neurons via palmitoyl side chains located in the central region of the molecule, and together with syntaxin and the synaptic vesicle protein VAMP/synaptobrevin constitutes the initial SNARE docking complex for regulated exocytosis. Clostridial toxins, which specifically cleave SNAP-25 have unequivocally demonstrated the requirement of the protein for vesicle exocytosis.^{1–3} Furthermore generation of SNAP-25 null mutant mice revealed that SNAP-25 is essential for evoked synaptic transmission, although it is not required for stimulus-independent neurotransmitter release.⁴ Besides its well characterized role in regulating exocytosis, there is increasing evidence that SNAP-25 also modulates various voltage gated ion channels.^{5–6} In particular, SNAP-25 interacts with different types of voltage-gated calcium channels (VGCCs), including N type,⁷ P/Q type,^{8,9} and L type,¹⁰ through a channel region known as the synaptic protein interaction (synprint) site. In line with these data, SNAP-25 negatively controls neuronal calcium responsiveness to depolarization¹¹ by specifically inhibiting, upon phosphorylation of Ser 187, neuronal VGCCs.¹² SNAP-25 therefore represents a multifunctional synaptic protein that plays an

essential role in synaptic vesicle fusion and modulates calcium dynamics in response to depolarization (fig. 1). Recently, evidence has accumulated that suggests that SNAP-25 is involved in different neuropsychiatric and neurological disorders. The present review summarizes this recent literature which indicates that the altered expression of the protein may produce abnormal behavioral phenotypes, including schizophrenia, attention-deficit/hyperactivity disorder and epilepsy.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

Attention-deficit/hyperactivity disorder (ADHD, MIM- Mendelian Inheritance in Man-143465) is one of the most prominent childhood neuropsychiatric disorders. It affects roughly 1 in 20 school-aged children in the U.S.,¹³ although a recent analysis reveals an even higher worldwide prevalence of 8-12%,¹⁴ with boys affected three or four times as frequently as girls.¹⁵ The major symptoms are persistent age-inappropriate behaviours of inattention and/or impulsivity and hyperactivity. As many as two thirds of children with ADHD have co-morbid disorders including language and communication deficits, disruption of learning and memory, anxiety and mood disorders and Tourette's syndrome.¹⁶ In about half of affected individuals, ADHD persists through adolescence into adulthood with deleterious effects on educational, social and occupational outcomes and a higher risk of developing substance abuse.^{14,17} One of the more striking aspects of ADHD is its clear inheritance, reflected by a 2-8 fold increased risk for either parents or siblings of ADHD-diagnosed individuals, and an estimate of 76% heritability based on twin studies.¹⁸ Several candidate genes have been implied and confirmed by linkage analysis. The multiplicity of these genes supports the idea that the biological heterogeneity may be a central factor to the clinical variability of the disorder. A number of studies have also implicated the role of environmental factors, which have been estimated to account for the additional variability in penetrance reported in twin studies.¹⁷⁻¹⁹ These environmental stressors have been shown to include maternal exposure to alcohol and smoking during pregnancy, head injury, obstetric complications and possibly lead exposure.¹⁵

The majority of genes evaluated for ADHD are involved in neurotransmission mediated by biogenic amines -dopamine, noradrenaline, and serotonin.¹⁸ The rationale for focusing on these genes is drawn largely from the well-documented therapeutic benefit of psychostimulant medication (e.g., methylphenidate and amphetamine) in ameliorating the behavioral impairments associated with ADHD.²⁰ Meta-analysis of linkage studies in case-controlled and family-based studies provide consistent evidence for the involvement of the dopamine D4 and D5 receptors, dopamine transporter, the synthetic enzyme dopamine β -hydroxylase, the serotonin transporter and HTR1B receptor.¹⁸ Among these genes, only those encoding for D4 receptor^{21,22} and the dopamine transporter²³ have been tested in mouse genetic models. These studies found significant neurochemical and behavioural effects only in homozygous null mutants.

SNAP-25 IN ADHD

Besides the biogenic amine candidate genes, the gene encoding SNAP-25 has been identified as responsible for hyperkinetic behaviour based on analysis of the *coloboma* mutant mouse. This mutant mouse is heterozygous for a neutron irradiation induced, semi-dominant deletion mutation spanning 4.6 Mb on mouse chromosome 2 that encompasses 10-12 genes, including *Snap25*.²⁴ In *coloboma* mutant mice (*Cm/+*), deletion of the *Snap25* gene results in 50% lower amounts of the SNAP-25 mRNA and protein expression compared to wild-type mice. Interestingly, *coloboma* mutant mice possess several phenotypic characteristics that parallel ADHD symptoms. *Coloboma* mice exhibit normal circadian rhythm and, as children with ADHD, they are hyperactive during their active (nocturnal) phase, with locomotor activity averaging three fold the activity of control

littermates.²⁵ Two key observations have led to the proposal that this mutant with reduced level of SNAP-25 expression represents a model for at least the hyperkinetic component of ADHD: 1) the hyperactivity was ameliorated by a low dose (4mg/kg, i.p.) of the psychostimulant amphetamine (AMPH), and 2) genetic rescue of the hyperactivity (but not the eye defect, or head bobbing) was obtained by crossing the mutant with SNAP-25 overexpressing transgenic mice.²⁴ Interestingly, transgenic rescue of SNAP-25 function also restores normal dopaminergic transmission.²⁶ Based on this first observation and supported by further behavioural and neurochemical analyses in the *coloboma* mutant mouse,²⁷⁻³² polymorphisms at the *SNAP25* gene locus in humans have been examined and association of SNAP-25 with ADHD has been determined in a number of linkage studies, ³³⁻³⁹ a finding that has been further confirmed by meta-analysis.¹⁸

SCHIZOPHRENIA

Schizophrenia (MIM 181500) is a common mental disorder with a prevalence of approximately 0.5-1%¹³ and significant heritability estimated about 85%.⁴⁰ The clinical symptoms can be classified into two main categories: psychotic or 'positive' symptoms, including hallucinations, altered emotional activity, and disorganized behaviour, and 'negative' symptoms, such as delusions, reduced interest and motivation and cognitive impairment. The disorder usually has its onset in early adulthood, although often cognitive and behavioural signs are present from childhood. Despite pharmacological treatments, outcomes are variable and approximately two-thirds of affected individuals have persistent symptoms with only partial remission.¹³ Schizophrenia is thought to be a neurodevelopmental disease characterized by defective connectivity in various brain regions during early life.⁴¹⁻⁴³ The neuropathophysiology of schizophrenia remains unclear, although alterations in dopaminergic and serotonergic circuitry (as in the case of ADHD), as well as in glutamatergic transmission have been strongly implicated. Numerous genetic linkage and association studies have identified regions of the genome that may harbor schizophrenia risk genes, but the complex genetics and symptomatology of the disease have limited progress in achieving a clear identification of the specific genetic determinants responsible for neurophysiological deficits that underpin the disorder.⁴⁴ Candidate genes that have been shown to be potentially associated with the disease include neuregulin, a protein belonging to the EGF family; dysbindin, a protein constituent of the dystrophin-associated protein complex; Catechol-o-methyltransferase (COMT), one of several enzymes that degrade catecholamines; the DISC1 (Disrupted-in-Schizophrenia-1) encoding a brain protein likely to play a role in cytoskeletal scaffolding; RGS4 (Regulator of G-protein Signaling 4) that modulates the GTPase activity of heteromeric G-proteins; GRM3, a metabotropic glutamate receptor; and the gene G72, which encodes a protein in brain thought to modulate NMDA glutamate receptor function.⁴⁵ All these findings have led to the view of schizophrenia as a disorder of connectivity and synaptic signalling.⁴⁴

SNAP-25 IN SCHIZOPHRENIA

A recent meta-analysis of 20 separate genome-wide linkage scans for schizophrenia-susceptibility genes reported significant linkage to the chromosomal region 20p12.3-11, which contains *SNAP25*, and suggested 20p12.3-11 as a strong candidate region for the disease.⁴⁶ Evidence from several immunohistochemical and Western blot studies in postmortem brains implicated reductions in SNAP-25 expression in the etiology of schizophrenia. Decreased levels of SNAP-25 were found in the hippocampus^{47,48} and in the frontal lobe Broadman's area 10 of patients with schizophrenia in comparison with controls.⁴⁹ In contrast, elevated levels of SNAP-25 were found in prefrontal lobe Broadman's area 9/49 and cingulate cortex.⁵⁰ It has been suggested that these discrepancies in altered expression between different brain regions may not only reflect the depressed functionality of certain neural circuits, but also the hyperactivity of other pathways that may

possibly result from compensatory mechanisms elicited through the neuropathophysiology of this disorder.⁴⁸

The analysis of two genetic models has recently supported the involvement of SNAP-25 in the neuropsychopathology of schizophrenia. First, the mutant hDISC1 transgenic mouse, which has been proposed as an animal model of schizophrenia characterized by spontaneous locomotor activity, impaired spatial reference memory evaluated in the Morris water maze and abnormal social interaction, as shown by the decreased social non-aggressive activity, has been recently shown to lead to a significant reduction of SNAP-25 expression.⁵¹ Second, a chemical mutagen induced dominant mutation (I67T missense) in a highly conserved domain of *Snap25* of the blind-drunk mutant mouse, appears to give rise to a schizophrenic phenotype that includes impaired sensorimotor gating, an important component of the schizophrenia phenotype related to altered sensory processing, anxiety and apathetic behaviors - phenotypic elements which appear to replicate aspects of the negative symptomatology of the disease.⁵²

EPILEPSY

Epilepsy is a group of heterogeneous neurologic disorders affecting almost 1% of the population. It is characterized by recurrent, unprovoked episodes of seizures, due to abnormal synchronous firing of groups of neurons, arising from periodic neuronal hyperexcitability. Clinical manifestations of epilepsy are varied and despite availability of a number of antiepileptic drugs, about one-third of epileptic patients are resistant to treatment. Several changes can occur in the brain undergoing pathological hyperactivity, at the level of both single cells and anatomically defined neuronal networks. Based on electroencephalographic recordings, seizures can be classified in focal (originating in a single area of the brain) or generalized (involving both brain hemispheres). Generalized epileptic syndromes can be classified as symptomatic (caused by identifiable factors) or idiopathic (without a clear etiology and partially caused by genetic defects).⁵³ Generalized idiopathic epilepsies include childhood absence epilepsy and juvenile absence epilepsy. These are characterized by a short, sudden impairment in consciousness and behavioral arrest, possibly accompanied by facial clonus. The electroencephalographic hallmark of absence epilepsy are spike-wave discharges (SWDs) that occur in the thalamo-cortical circuitry. Mutations in different genes, including genes codifying for GABA receptors, Na⁺, K⁺, and Ca²⁺ channels, have been associated to the familial forms of generalized idiopathic epilepsy with a Mendelian inheritance.⁵⁴⁻⁵⁶ Analysis of absence epilepsy mouse models *tottering/tg*, *lethargic/lh* and *stargazer/stg*, bearing mutations in $\alpha 1A$, $\beta 4$, $\gamma 2$ Ca²⁺ channel subunits respectively, revealed altered high voltage activated (HVA) channels current density in *tg* and *stg* thalamic neurons, and increased low voltage activated (LVA) channels peak current and a depolarized shift of the steady-state inactivation curves in *tg*, *lh* and *stg* thalamic neurons.⁵⁷ Furthermore, the association of mutations in human $\alpha 1A$ (P/Q type) channels with absence epilepsy has been reported.⁵⁸

SNAP-25 IN EPILEPSY

Interestingly, the mutant mouse *coloboma* (*Cm/+*), which has been implicated as a model of ADHD (see above), has also provided evidence for the involvement of SNAP-25 in epilepsy. In addition to their hyperkinetic activity, *Cm/+* mice display frequent spontaneous bursts of bilateral cortical SWDs that are accompanied by behavioral arrest, which is typical of absence epilepsy. These seizures could be completely blocked by intraperitoneal injection of the antiepileptic drug ethosuximide.⁵⁹ Analysis of calcium current amplitude in thalamocortical neurons of this mutant, moreover, revealed an increase in the peak current density of LVA currents in *Cm/+* cells compared to wild type mice. It is important that this calcium increase is not itself seizure-induced, as it precedes the developmental onset of

SWDs,⁵⁹ suggesting that the seizures may arise from abnormalities in calcium transients caused by a SNAP-25 deficiency in modulating presynaptic voltage-gated calcium channels.¹²

CONCLUSIONS

SNAP-25 is a multifunctional synaptic protein that plays an essential role in neurotransmitter release via the formation of the SNARE complex⁴ and modulates calcium dynamics in response to depolarization.^{11,12} While recent genetic studies of human populations, and of some mouse models do implicate that alterations in SNAP-25 gene structure, expression and/or function may contribute directly to these distinct neuropsychiatric and neurological disorders, in other cases changes in SNAP-25 may represent a consequence of the neuropathologies of disease. Under this circumstance, effects on SNAP-25 expression could be downstream and secondary to maintaining synaptic homeostasis, resulting from altered neural circuits or network function, or from more general perturbations to brain development. Moreover, genetic studies have also revealed that candidate genes associated with neuropsychiatric disorders, including *SNAP25*, appear to contribute only a small effect towards the overall phenotype of disability (as reviewed in ref. 18 for ADHD). Consequently, these genetic components are likely to reflect susceptibility genes that act together and in concert with environmental factors to affect the broad spectrum of deficits associated with mental health disorders. Further studies are required, therefore, to delineate the potential mechanisms through which alterations in SNAP-25 may play a direct role in the etiology as well as contribute to the pathology of ADHD, schizophrenia, epilepsy and possibly other neuropsychiatric disorders.

Acknowledgments

Supported by EUSynapse Integrated Project, Telethon GP04196, Cariplo 2006.0779/10.9251, Compagnia di S.Paolo (Prog. 2005.1964) (M.M), and by National Institutes of Health Grant MH48989 (M.C.W.)

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Figure 1.