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Review

SNARE proteins and schizophrenia: linking synaptic and neurodevelopmental hypotheses

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Much of the focus of neurobiological research into schizophrenia is based on the concept that disrupted synaptic connectivity underlies the pathology of the disorder. Disruption of synaptic connectivity is proposed to be a consequence of both disrupted synaptic transmission in adulthood and abnormalities in the processes controlling synaptic connectivity during development of the central nervous system. This synaptic hypothesis fits with neurodevelopmental models of schizophrenia and our understanding of the mechanisms of antipsychotic medication. This conceptual model has fostered efforts to define the exact synaptic pathology further. Synaptic proteins are obvious candidates for such studies, and the integral role of the SNARE complex, and SNARE-associated proteins, in synaptic transmission will ensure that it is the focus of much of this research. Significant new insights into the role of this complex are arising from new mouse models of human disease. Here the evidence from both animal and human clinical studies showing that the SNARE complex has a key role to play in the aetiology and pathogenesis of schizophrenia is discussed.

Keywords: schizophrenia, SNARE, Snap25, syntaxin, synaptobrevin, genetics, mouse mutants

INTRODUCTION

The processes involved in the development of the schizophrenic phenotype are complex and although numerous theories have been put forward several hypotheses have predominated. The dopamine hypothesis of schizophrenia arose from observations that dopamine agonists induce psychosis and that antipsychotic medications block dopamine receptors. The schizophrenic phenotype was, therefore, attributed to a hyperdopaminergic state (Melzer & Stahl, 1976). This hypothesis has been modified so that schizophrenic psychosis is attributed to hyperactive dopaminergic transmission in the basal ganglia, and cognitive decline is attributed to underactive dopaminergic transmission in prefrontal areas (Keshavan, 1999). Other neurotransmitters have been implicated including glutamate. The glutamate hypothesis developed in a similar fashion to the dopaminergic hypothesis. Glutamate levels were found to be reduced in schizophrenic patients and glutamate antagonists were observed to precipitate a schizophreniform psychosis in normal subjects (Kim *et al.*, 1980; Kornhuber, 1992). Indeed, alterations in glutaminergic transmission may be result in the observed alterations in dopaminergic activity. In addition to these more mainstream neurotransmitter hypotheses, other molecular mechanisms have been implicated in schizophrenia including abnormalities in ion channel function, immunological processes and mitochondrial physiology (Dworakowska *et al.*, 2000).

The synaptic hypothesis of schizophrenia has arisen predominantly from the dopaminergic and glutaminergic transmitter hypotheses and neurogenetic studies which have implicated genes which influence synaptic transmission (Owen *et al.*, 2005). The complexity of processes underlying the schizo-

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Abbreviations: CSF, cerebrospinal fluid; NSF, *N*-ethylmaleimide sensitive factor; PPI, pre-pulse inhibition; SNP, single nucleotide polumorphism; SNAP, synaptosomal-associated protein; SNARE, Soluble *N*-ethylmaleimide-sensitive factor (NSF) attachment protein receptor; VAMP, vessicle-associated membrane protein.

phrenic phenotype is also highlighted by epidemiological studies which suggest that processes early in development, perhaps even *in utero*, are involved in the pathogenesis of schizophrenia. Linkage and association studies appear to support the idea that a genetic vulnerability for schizophrenia exists in individuals who carry a cluster of genes. This has led to a neurodevelopmental hypothesis of schizophrenia which posits that pathogenetic biological events or characteristics are present much earlier in life than the onset of the features of the illness (e.g., psychosis) required for diagnosis.

The hypothesis was proposed by a number of groups in the 1980's (Church *et al*., 2002) and Weinberger (1987) proposed that schizophrenia is a "neurodevelopmental disorder in which a fixed brain lesion from early life interacts with certain normal maturational events that occur much later." In essence, environmental factors affect causative gene clusters to precipitate a schizophrenic phenotype in susceptible individuals. The fundamental concept here is that a "brain lesion can remain clinically silent until normal developmental processes bring the structures affected by the lesion 'on line'" (Weinberger, 1987). The resulting lesion in the mature adult brain may be aberrant functional connectivity in the neuronal circuit, thus fitting well with the synaptic hypothesis of schizophrenia. A combined neurodevelopmental and synaptic hypothesis offers a neat conceptual framework to which hypotheses regarding genetic predisposition and environmental insults can lead to aberrant synaptogenesis and continued dysfunction of mature synapses can be applied. An increasing body of evidence has placed the docking machinery of synaptic vesicle exocytosis at the centre of this synaptic hypothesis.

Quantal neurotransmitter release is brought about by the cyclic docking and un-docking of synaptic vesicles with the pre-synaptic membrane. Soluble *N*-ethylmaleimide sensitive factor (NSF) attachment protein receptor (SNARE) proteins form a complex which is essential for the docking of synaptic vesicles. There are three membrane-associated SNARE proteins characterized by a homologous 70-residue sequence known as the SNARE motif. The synaptosomal-associated protein of 25 kDa (SNAP-25) and syntaxin-1A interact with the vesicle-associated membrane protein (VAMP-2, also known as synaptobrevin) to create a stable ternary core complex with 1:1:1 stoichiometry (Sollner *et al*., 1993). The formation of the SNARE complex brings vesicle and presynaptic terminal membranes together so that fusion and neurotransmitter release can occur. The SNARE proteins interact with a number of other proteins, such as α-SNAP and the complexins, which modulate this sequence of events (see Sudhof, 1995 and 2004 for comprehensive reviews). One of the major SNARE-interacting proteins is synaptotagmin is a calcium sensor that promotes vesicle fusion with the presynatpic terminal through its interaction with the SNARE complex (Martens *et al*., 2007). Another SNARE-modulating presynaptic protein is dysbindin which has been shown to modulate the expression of the SNAP-25, possibly *via* an interaction with snapin (Numakawa *et al*., 2004; Talbot *et al*., 2006). Dysbindin is particularly interesting it has been suggested that it may modulate dopamine release in the central nervous system *via* an effect on the SNARE complex (Kumamoto *et al*., 2006). The synapsin family is another group of three presynaptic phosphoproteins (synapsin 1, 2 and 3) which are involved in regulation of synaptic vesicle release although a direct interaction with the SNARE complex has yet to be fully elucidated. Phosphorylation of synapsin proteins is thought to release a reserve pool of synaptic vesicles making them available for release of neurotransmitter thus increasing the strength of synaptic transmission. The synapsin family appears to play a role in neurogenesis and neuronal development which would make plausible molecular candidates in a neurodevelopmental model of schizophrenia (Ferreira *et al*., 2000).

There is an increasing body of evidence from neuropathological studies, human genetic studies, and animal studies that the SNARE complex may play a role in the aetiopathology of schizophrenia. We propose that the SNARE complex may represent a pathway through which genetic factors may influence the expression of the schizophrenic phenotype.

SNARE PROTEINS IN THE NEUROPATHOLOGY OF SCHIZOPHRENIA

Although there is no overt neuropathology in schizophrenia, several structural brain changes have been described, most notably ventriculomegaly and smaller hippocampi (Chaturvedi & Thakur, 2003). However, these changes are not pathogenic and may reflect sub-types of patient, e.g., these changes may reflect atrophy in patients who also have a component of clinical dementia. Significantly, there is no gliosis, thus excluding neurodegeneration as a pathological mechanism. Electron microscopy studies have revealed ultrastructural changes in the synaptic organisation of several brain regions in schizophrenic patients (Miyakawa *et al*., 1972). Subtle abnormalities of neuronal organisation and synaptic connectivity appear to be the most prominent pathological features of schizophrenia (Arnold & Trojanowski, 1996). These neuropathological features appear to be most prominent in the hippocampus, the thalamus and the dorsolateral prefrontal cortex and Harrison and Weinberger have outlined how these features

have fostered the view that schizophrenia is a disorder of synaptic connectivity (Harrison & Weinberger, 2005). They have speculated that genetic factors influence the schizophrenic phenotype by a functional effect on synaptic plasticity and the development of cortical microcircuitary. They have labelled this functional effect of genes at the level of the synapse, the 'genetic cytoarchitecture' of the underlying pathology. There is and increasing amount of evidence that the SNARE complex is likely to be a core component if this 'genetic cytoarchitecture'.

Post mortem studies have revealed changes in the expression of presynaptic proteins (resolved at the RNA and protein levels). The direction of expression changes vary between brain regions and findings are not always consistent between groups. Findings of various groups are summarised in Table 1. Significantly, the changes do not appear to be due to altered synaptic densities, consistent with an alteration of the presynaptic machinery rather than in the number of synapses *per se.*

Honer *et al.* (2002) carried out a semi-functional study by using immuno-blotting to examine the interactions of the three core SNARE proteins in the frontal cortex of patients with schizophrenia and depression. It was found that in subgroups with suicide as a cause of death, relatively more SNAP-25 and syntaxin was present in the heterotrimeric SNARE complex than in other molecular forms. The authors hypothesized that these abnormalities in the SNARE complex may represent a molecular substrate for abnormalities of neural connectivity in severe mental disorders.

Several SNARE-interacting proteins have been studied in pathological studies of brains from schizophrenic patients. Synaptophysin in particular is well established as a marker of synaptic pathology (Masliah *et al*., 1990) and its expression has been looked at in a number of brain regions. Synaptophysin binds synaptobrevin and has been implicated as a potential molecular control of synaptic exocytosis (Edelmann *et al*., 1995). Protein and mRNA studies of synpatophysin have shown that its expression is reduced in some, but not all regions, of the cerebral cortex, hippocampus and cerebellum of schizophrenic subjects (Eastwood & Harrison, 1999; Karson *et al.,* 1999; Eastwood *et al*., 2000; 2001). Related studies have found similar changes in the expression of the complexins (Sawada *et al.,* 2002; Eastwood *et al.,* 2001), but not for NSF (Imai *et al*., 2001). In addition to SNARE-associateed proteins, synapsin 3, a member of the synapsin family which is known to modulate synaptic vesicle release, has been found to be reduced in the prefrontal cortex of schizophrenic subjects (Porton & Wetsel, 2007).

There has been at least one microarray study which has shown alteration in the expression of SNARE-interacting proteins. Mirnics *et al*. (2000) carried out microarrays in ten schizophrenic patients and found that expression of *N*-ethylmaleimide sensitive factor and synapsin II were reduced in the prefrontal cortex of almost every patient. Also, a single expression array found that syntaxin mRNA increased 4 fold in the entorhinal cortex of schizophrenic patients, although reduced SNAP-25 was found in entorhinal cortex layer II stellate neurones (Hemby *et al*., 2002).

Findings from the various expression studies of SNARE proteins carried out in schizophrenics are not easily comparable due to varying methodologies of expression analysis, different patient demographics, and the different anatomical loci chosen as a focus of study. Nonetheless, alterations in this core synaptic machinery seem to be a consistent component of the neuropathology of this disorder. The question has been raised as to whether alterations in the expression of the SNARE proteins, and their SNARE-interacting proteins, reflect an overall abnormality of synapse connectivity, or whether they represent more subtle changes in the control of the synaptic vesicle exocytotic machinery and hence synapse functionality (Harrison, 2004). However, studies which show differential changes in the expression of vesicle proteins within the same patient group (Eastwood *et al.,* 2001) point towards changes in SNARE-mediated functions. Antipsychotic medication does not appear to be a significant factor causing changes in synaptic protein expression in schizophrenia (Harrison, 1999). Furthermore, it has been suggested that SNARE proteins may, in fact, be a molecular substrate for the clinical effects of antipsychotics (Barr *et al*., 2006).

SNARES IN HUMAN GENETIC STUDIES OF SCHIZOPHRENIA

More than 20 genome-wide scans aiming to localize genes for schizophrenia have been reported and several meta-analyses have been completed producing a list of at least 12 strong candidate genes (Gogos & Gerber, 2006). Many of the genes identified are known to have central roles in synaptic function, e.g., the proline dehydrogenase (*PRODH*) gene located on chromosome 22q11 (Karayiorgou *et al*., 1995); the dystrobrevin-binding protein 1, or dysbindin, (*DTNBP1*) gene which is located on chromosome 6p (Straub *et al*., 2002); neuregulin 1 (*NRG1*) on chromosome 8p (Stefansson *et al*., 2002); and the catechol-*O*-methyltransferase (*COMT*) gene located in the 22q11 locus (Shifman *et al*., 2004). There are also a number of studies which support a role of the SNARE complex in the genetic basis of schizophrenia. A single nucleotide polymorphism (SNP) in

Table 1. Summary of expression studies of SNARE complex proteins at both the RNA and protein level in human schizophrenic subjects

Method of expression analysis	SNARE/SNARE-interacting proteins examined	Patient sample	Brain regions examined	Findings	Reference
ELISA, immunoblotting and immunohistochemistry	SNAP-25 Synatxin Synaptophysin	18 schizophrenic patients 24 controls	Cingulate cortex	Levels of syntaxin were increased in cingulated cortex of schizophrenics, but no changes in levels of SNAP-25 or synaptophysin were seen	Honer *et al.*, 1997
Immunoreactivity	SNAP-25 Syntaxin Synaptophysin	19 elderly subjects with schizophrenia 16 elderly controls	Cingulate cortex Parietal, temporal and frontal cortex	Levels of SNAP-25, syntaxin, and synaptophysin were increased in the cingulate cortex of schizophrenic patients, and decreased in the parietal, temporal and frontal cortices of Alzheimer's patients	Gabriel *et al.*, 1997
ELISA and quantitative immunocytochemistry	SNAP-25	13 schizophrenic patients 13 age-matched controls	Hippocampus	No overall change in SNAP-25 expression seen by ELISA of the whole hippocampus. However, immunocytochemistry revealed significant reductions of SNAP-25 in the terminal fields of entorhinal projections (subiculum, CA1, CA3, CA4 and dentate gyrus)	Young *et al.*, 1998
Quantitative dot immunoblotting of cerebrospinal fluid	SNAP-25	8 schizophrenic patients 4 patients with headache 5 bipolar patients	Cerebrospinal fluid (CSF)	Levels of SNAP-25 increased in CSF of schizophrenics compared to other groups	Thompson *et al.*, 1999
Western blotting and Northern analysis of mRNA	SNAP-25 Synaptophysin	14 schizophrenic patients 12 controls	Brodmann's area 10 of prefrontal cortex	Protein levels of SNAP-25 and synaptophysin reduced in schizophrenics but no changes at mRNA level	Karson *et al.*, 1999
Quantitative PCR of mRNA levels	SNAP-25 Syntaxin 1 Synaptobrevin 1 Synaptobrevin 2	14 elderly schizophrenic patients 9 age-matched controls	Left temporal gyrus (Brodmann's area 22)	Levels of syntaxin and SNAP-25 decrease with age in schizophrenic patients	Sokolov *et al.*, 2000
Quantitative IHC and immunoblotting	SNAP-25 Syntaxin Synaptobrevin	15 schizophrenic patients 12 unipolar depressive patients 13 bipolar patients 15 controls	Ventral hippocampus	Levels of SNAP-25 reduced by 51% in the stratum granulosum of schizophrenic patients and by 45% in stratum oriens of bipolar patients. SNAP-25 levels were increased by 54% in the presubiculum of depressed patients	Fatemi *et al.*, 2001
ELISA Immunoblotting	SNAP-25 Syntaxin Synaptobrevin	7 patients with schizophrenia and suicide 6 patients with schizophrenia who died of causes other than suicide 11 patients with depression and suicide 15 controls	Superior, middle and inferior frontal gyrus	Increased levels of SNAP-25 and syntaxin in heterotrimeric complex in groups of schizophrenics and depressives with suicide as the mode of death Levels of SNAP-25 reduced by 28% in schizophrenics who died of causes other than suicide	Honer *et al.*, 2002

Competitive ELISA and immunohistochemistry	SNAP-25 Syntaxin Synaptophysin	8 schizophrenic patients 8 controls	Cerebellum (Superior/inferior semilunar and gracile lobules)	Selective loss of SNAP-25 in schizophrenic cerebellar tissue without a decrease in synaptophysin	Mukaetova-Ladinska *et al.*, 2002
Western blotting	SNAP-25	7 schizophrenic patients 4 bipolar patients 8 controls	Whole hippocampus	Levels of SNAP-25 were reduced by 49% in schizophrenics	Thompson *et al.*, 2003a
Quantitative dot immunoblotting of cerebrospinal fluid	SNAP-25	25 schizophrenic patients 25 control patients 19 of the schizophrenic patients received haloperidol for 3 months and then 3 months of placebo	Cerebrospinal fluid (CSF)	Levels of SNAP-25 were increased in the CSF of both haloperidol and placebo groups of schizophrenics. There was also positive correlation between the amount of SNAP-25 in the CSF and measures of severity of psychosis	Thompson *et al.*, 2003b
Quantitative immunoblotting	Synaptobrevin SNAP-25	22 schizophrenic patients 18 controls	Prefrontal cortex	Synaptobrevin reduced by 22% in prefrontal cortex of schizophrenic subjects. There was no change in SNAP-25	Halim *et al.*, 2003
Western blot analysis and real-time polymerase chain reaction	SNAP-25 Synaptophysin	20 schizophrenic patients 8 bipolar disorder patients	Brodamann's area 9 of dorsal prefrontal cortex	Both SNAP-25 and synaptophysin were increased in bipolar patients, but no changes were seen in schizophrenic patients	Scarr *et al.*, 2006

intron 7 of syntaxin 1a has been found to be associated with schizophrenia in a sample of 238 nuclear families (Wong *et al*., 2004). Association studies with SNAP-25 studies have been conflicting (Tachikawa *et al*., 2001), but meta-anlysis reveals SNAP-25 to be in a strong candidate region for schizophrenia (Lewis *et al*., 2003) and there is evidence that suggests SNAP-25 may be associated with clinical response to antipsychotics (Muller *et al*., 2005). There has been no association study with synaptobrevin to date. However, association has been found for the complexins which interact with and modulate SNARE function complexin (Lee *et al*., 2005). In addition, a member of the synaptotagmin family, synaptotagmin XI (*Syt 11*), is located on chromosome locus 1q21-q22, which has been reported as a susceptibility locus for schizophrenia (Inoue *et al*., 2007).

The synapsin 2 gene (*Syn2*) locus on chromosome 3p25 has been associated with schizophrenia in Northern European families (Saviouk *et al*., 2007). The synapsin 3 gene (*Syn3*) may also be associated with schizophrenia in the African American population (Porton *et al*., 2004; Lachman *et al*., 2005). In addition, one of the strongest linkages with schizophrenia has been found for dysbindin (Straub *et al*., 2002; Schwab *et al*., 2003). It seems likely, therefore, that SNARE proteins will be important in modulating the function of other mutated genes implicated in the schizophrenic phenotype.

Association studies of the SNARE complex, therefore, indicate that at least two of its components, syntaxin 1a and SNAP-25, are candidate genes for schizophrenia. In addition several SNARE-associated proteins have associations with the disease, including dysbindin, complexin and synaptotagmin. This raises the possibility that the SNARE complex may act as a common final pathway whereby the functional synaptic abnormalities of schizophrenia are modulated. SNARE-associated proteins may act as regulators, or molecular switches, controlling SNARE complex assembly and disassembly. They may provide a mechanism by which second messenger systems may affect vesicle exocytosis by responding to changes in intracellular calcium and phosphorylation states.

BEHAVIOUR OF SNARE MOUSE MUTANTS

There are an increasing number of studies which show that modulation of the SNARE complex cause behavioural changes in mice that may be relevant to human psychiatric disease. Single-gene knock-out murine mutants have been engineered for Snap-25 (Washbourne *et al*., 2002) and synaptobrevin 2 (VAMP2) (Schoch *et al*., 2001), although both lines were postnatally lethal. Snap-25 -/- fetuses develop

until birth with no overt phenotypic abnormalities, although they can be distinguished from heterozygotes and wild-types between E17.5 and E18.5 by a distinct tucked posture and inactivity (Washbourne *et al*., 2002). Although Snap25 -/- hearts contract post-natally they do not make any respiratory effort and it is thought that they die of respiratory failure (Molnár *et al*., 2002). Homozygous synaptobrevin 2 knock-out mice also die immediately post-natally although the only obvious defect is a small morphological change by way of a small shoulder hump thought to represent a collection of brown fat (Schoch *et al*., 2001). No abnormal phenotype has been reported for either the Snap25 or the synaptobrevin 2 knock-out mice in the heterozygous form but, to date, neither of these lines has been subject to extensive behavioural phenotyping. More recently a gene knockout for syntaxin 1a was generated (Fujiwara *et al*., 2006). Although the syntaxin 1a knockout performs normally in spatial memory tasks in a conditioned fear paradigm, both consolidation and fear memory extinction were impaired. That this may be due to an impairment of synaptic plasticity, supported by findings of impaired long-term potentiation in hippocampal slices, despite normal synaptic transmission in hippocampal cell cultures. The viability of the syntaxin 1a knockout mouse is likely to be due to the compensatory effects of syntaxin 1b in this line.

Most recently, a *Snap*-25 mutant mouse, known as *'blind-drunk'* due to its characteristic ataxic gait, has been shown to have a deficit in pre-pulse inhibition (Jeans *et al*., 2007), a sensorimotor gating endophenotype associated with schizophrenia (Gould *et al*., 2004). The blind-drunk mutant is a single T to C transition in codon 67 of *Snap*-25, resulting in an isoleucine to threonine substitution (Jeans *et al*., 2007). The *Bdr* mutation has been shown to disrupt binding characteristics of Snap-25 to the SNARE complex and alter central neurotransmission without any overt neuropathological changes. Rotarod testing of the blind-drunk revealed a deficit of more than 30% at 7 weeks and 6 months in blind-drunk compared to littermate controls, a finding consistent with an ataxic phenotype (Jeans *et al*., 2007). In addition, pre-pulse inhibition (PPI) testing revealed a small but robust (10–15%) deficit in mutants compared to controls at the same time points. The blind-drunk mouse has also been found to have subtle defects in higher cerebral functions as evidenced by deficits in paradigms of exploratory behaviour, social interaction and light/dark anxiety testing compared to controls (Jeans *et al*., 2007).

Another mutant with relevance to the SNARE complex is the coloboma mouse mutant which has a contiguous deletion of 4 genes (*Plcβ*-1, *Plcβ*-4, *Snap*-25, and *Jag*-1) on chromosome 2 (Hess *et al*., 1992; 1994). The *Cm* deletion is embryonic lethal when homozgote (Theiler *et al*., 1981). However, adult heterozygous mice (*Cm*/+) exhibit a robust phenotype which includes hyperactive locomotor activity, head bobbing, and ocular dysmorphology — sunken and often closed, eyes (Searle, 1966). The hyperactivity of *Cm*/+ is three fold greater than littermate controls (Wilson, 2000). This hyperactivity is first seen between post-natal day 11 and 14 and was preceded by deficits in neurodevelopmental milestones such as the righting reflex and bar-holding (Heyser *et al*., 1995). The *Cm*/+ phenptype has been extensively characterised and as the hyperactivity is ameliorated by low doses of D-amphetamine it has been proposed as model of attention deficit hyperactivity disorder (Hess *et al*., 1996). Although, it is possible that the *Cm*/+ phenotype is due to any or a number of the genes in the deleted segment evidence has been presented to implicate *Snap*-25. Expression of Snap-25 protein in *Cm*/+ is only 50% of that in wild-types which would be consistent with a dose-dependent decrease due to loss of one allele of *Snap*-25 at the *Cm* locus. Transgenic rescue with a *Snap*-25 minigene has been shown to rescue both the hyperactivity of *Cm*/+ and restore a normal amphetamine response (Wilson, 2000). It is interesting to note that neither the head-bobbing or ocular dysmorphology were affected by the *Snap*-25 transgene (Hess *et al*., 1996). It is likely, therefore, that these other traits in the Coloboma are determined by the other genes in the *Cm* locus.

Two additional mouse models relevant to the SNARE complex are the complexin I and complexin II knock-out mice. Complexins binds to the SNARE complex in a competitive manner with αSnap and may act to stabilise the SNARE complex (Reim *et al*., 2001). Complexins are particularly interesting as their expression has been found to be altered in the brain of both Huntington's and schizophrenic patients (Glynn *et al*., 2003). Knockout studies of the complexins in mice reveal that complexin I mice are ataxic whereas complexin II knock-out mice show much more subtle abnormalities of neurological function, including progressive cognitive and motor deficits (Glynn *et al*., 2003; 2005). Although complexins are not needed for synaptogenesis, or normal brain development, physiological studies show that they are regulators of synaptic vesicle exocytosis and that alteration in their expression has an effect on long term potentiation in the hippocampus (Takahashi, 1999; Reim *et al*., 2001). It is possible that the ataxic phenotype of the complexin knock-outs and blind-drunk mice may have conceptual implications regarding animal modelling of schizophrenia. Experimental modulation of schizophrenia candidate genes in mice may produce different phenotypes to that seen in humans. Andreasen has postulated that schizophrenia results

from an abnormality in cerebellocortical networks thus causing disordered thought: this is known as the cognitive dysmetria hypothesis (Andreasen *et al*., 1999). Andreasen's hypothesis of schizophrenia may mean that ataxia may not be such an unexpected phenotype after all. It may be that the genes involved in the development of these cerebellocortical circuits are involved in the development of similar neural pathways involved in motor coordination in rodents. If this is the case then it is conceivable that disruption of the function of these genes in mice would result in movement abnormalities such as ataxia. Furthermore, epidemiological studies suggest that that disrupted motor control may be an important precursor of schizophrenic illness (Guerra *et al*., 2002), and neurological soft signs, including gait ataxia, may be features of first episode schizophrenia (Boks *et al*., 2004). Indeed, phenotypic characteristics of available murine mutants some of the strongest schizophrenia susceptibility genes reveal a wide variation in the phenotypic characteristics of these mouse models. A *Prodh* knock-down model has been found to have PPI deficits, but no alterations in spontaneous alternation, nor any anxiety-type behaviours in light-dark testing (Paterlini *et al*., 2005). Mice deficient in *Nrg1* have been found to be hyperactive in open field paradigms and exhibit abnormalities in distinct elements of exploratory behaviour including deficits in habituation processes (O'Tuathaigh *et al*., 2006). There is, as yet, no *dysbindin* knock-out mouse, however, the *sandy* mouse (*sdy*) contains an in-frame deletion of two exons of the mouse *dysbindin* gene but no behavioural analysis of this mutant, including PPI, testing has not revealed any differences compared to wild-type controls (Li *et al*., 2003). Mice deficient in Disc1 protein during development have been found to have deficits in sociability and spatial working memory (Li *et al*., 2005)[1]. In light-dark testing of homozygous *Comt* knock-out mice female but not male mice spent significantly greater time within the light portion of the light–dark apparatus, indicating a putative sex-specific role for the *Comt* gene in the modulation of anxiety, however, there was no PPI deficit found in these mice (Gogos *et al*., 1998). As schizophrenia is almost certainly a polygenic disorder, altering the function of any single gene in mice is unlikely to produce all the phenotypic characteristics that might be considered to be endophenotypes of schizophrenia. Accepting that it may be possible, or even likely, that different phenotypes in mice can be considered as correlates of the human schizophrenic phenotype will require a significant paradigm shift. However, mutants such as the blind-drunk mouse, which exhibit features of ataxia and a concurrent PPI deficit, may facilitate this conceptual leap: same gene, different phenotype.

CONCLUSION

The SNARE complex is essential for the docking of synaptic vesicles at the presynaptic terminal in the central nervous system and modulation of this complex is likely to be an important aspect of the functional pathology seen in the central nervous system of schizophrenics. The SNARE complex and some of its associated proteins are known to be involved in neurogenesis, neural migration and synaptic transmission. The SNARE complex is, therefore, a plausible biological candidate as a final common pathway for the expression of the schizophrenic phenotype that fits in with both neurodevelopmental and synaptic hypotheses of schizophrenia. Changes in the expression of the SNARE complex and SNARE-interacting proteins have been found in the relevant brain regions in post-mortem studies of schizophrenic subjects. In addition, components of the SNARE complex and its interacting proteins have been found to be associated with schizophrenia in human genetic studies. Furthermore, behavioural phenotypes of murine SNARE mutants and SNARE-associated protein mutants may be relevant to the human schizophrenic phenotype. Known interactions of the SNARE complex with the neurotransmitter systems, such as the glutaminergic and dopaminergic systems, that are disrupted in schizophrenia add further weight to their putative involvement in this complex disorder. A combination of functional analysis, characterisation of SNARE mutations in mice, and further human genetic studies of the SNARE machinery is likely to help further elucidate the molecular and cellular mechanisms the neurodevelopmental and neurotransmitter abnormalities in schizophrenia.

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