Dysbindin-1 mutant mice implicate reduced fast-phasic inhibition as a final common disease mechanism in schizophrenia

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AUTHOR SUMMARY

Schizophrenia is a complex neuropsychiatric disorder characterized by a broad range of sensory, cognitive, and affective symptoms, many of which are resistant to treatment. Research attempting to understand the cause of the disorder has moved forward on two fronts: genetic and mechanistic. On one hand, recent studies have identified a diverse range of candidate genes that may put subjects at risk for schizophrenia (1). On the other hand, through clinical pharmacology, postmortem studies, and work in animal models, a number of neuronal mechanisms have been identified that likely underlie behavioral and sensory features of the disease. However, the actual mechanisms linking genetic differences to these features of schizophrenia have not been well-elucidated. To access the neuronal substrates of schizophrenia-associated phenotypes, we investigated systems and neuronal circuit electrophysiology in mice with reduced expression of dystrobrevin-binding protein 1 (dysbindin-1), a well-established genetic risk factor.

These mutant mice reproduced clinical auditory endophenotypes common to schizophrenia, including deficits in γ-synchrony, sensory gating, and prepulse inhibition. These abnormalities were associated with changes in local circuit dynamics, particularly abnormalities in parvalbumin-expressing interneurons and a loss of inhibition, which may explain clinical EEG features that are characteristic of schizophrenia.

Our research seeks to understand the neuronal mechanism of neuropsychiatric disorders, especially in identifying how changes in the interaction of different types of neurons (their circuitry) lead to symptoms of the disease. We primarily use mouse models of these disorders. The *gene dystrobrevin binding protein 1* (*Dys1*), which encodes the protein dysbindin-1, is a leading candidate gene for susceptibility to schizophrenia, and expression of dysbindin-1 is reduced in the majority of patients. Clinically, alternative forms of this gene are associated with disrupted spatial memory and abnormal sensory responses, which are recorded by EEG. In mice carrying a spontaneous mutation in the *gene dystrobrevin binding protein 1* gene (*Dys1*−/−), a number of functional deficits have been shown that point to disrupted neuronal signaling involving the neurotransmitters glutamate or dopamine (2). However, preclinical studies have yet to connect such signaling abnormalities to clinical deficits characteristic of schizophrenia, making it difficult to directly ascribe these abnormalities to symptoms of the disease. The current studies provide a unique link between a genetic risk factor and such disease symptoms by studying if disruptions of the neuronal circuitry that can generate high-frequency neuronal activity are disrupted by reductions in dysbindin-1.

Abnormalities in the activation of neurons involved in inhibition via release of the transmitter GABA are thought to be involved in schizophrenia. This idea arises in part from experiments targeting excitatory pathways in animal models and human subjects. Interference of signaling involving the excitatory inputs to the inhibitory cells, particularly through the administration of various drugs, has been extensively investigated as a preclinical model of schizophrenia. Such drugs are known to exacerbate the symptoms of schizophrenia, induce some similar symptoms as the clinical disorder in healthy subjects, and recapitulate core schizophrenia-like behavioral deficits in rodents. Additional studies have linked reduced NMDA receptor sig-

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naling in mice to decreased levels of the GABAergic interneuron marker parvalbumin (PV), a well-established clinical neuropathological finding, indicating that mouse models and schizophrenia may share disrupted inhibitory function.

Additionally, interest in the subset of inhibitory PV-expressing interneurons arises from their functional significance. The protein PV is expressed in fast-spiking inhibitory interneurons that are necessary to generate sensory-evoked, high-frequency cortical activity in the EEG γ-band (30–100 Hz) in response to sensory stimuli. Consistent with PV cell dysfunction as a key pathophysiological mechanism underlying schizophrenia, components of evoked γ-band activity are also reduced in schizophrenia (3). These observations and others have led to the GABAergic dysfunction hypothesis of schizophrenia (4).

Despite these findings, genetic risk factors have not aligned with the GABAergic hypothesis. Leading risk factors have, instead, led researchers to study mechanisms associated with dopamine and glutamate. As such, it is unclear whether the established genetic liability for schizophrenia, such as dysbindin-1 risk alleles, leads to GABAergic dysfunction. Using the Dys1−/− mouse, we asked if reduced dysbindin in these mice would lead to the same changes in auditory-evoked EEG abnormalities associated with loss of inhibition. Thus, we investigated whether the Dys−/− model could provide insight into circuit-level disruption, which could explain common endophenotypes of the disease. We found that Dys1−/− mice recapitulated a number of auditory-evoked EEG abnormalities associated with schizophrenia. Furthermore, we linked these differences with reduced PV expression in the auditory cortex and hippocampus of Dys1−/− mice. Thus, the reduction in dysbindin-1 in these mice seemed to replicate a set of features associated with schizophrenia, including the reduction of PV.

We next directly investigated the specific effects on signaling in the hippocampus to identify the type of neuronal interactions that may underlie the schizophrenic-like symptoms of the Dys1−/− mice by using voltage-sensitive dye imaging. In area CA1 of the hippocampus, most of the excitable membrane is composed of pyramidal cell dendrites (the principal cells of the hippocampus proper). These cells receive both excitatory and inhibitory input. Voltage-sensitive dye imaging observations (Fig. P1 A and B) showed that these mice had reduced inhibition signals but unaffected excitatory signals. In Dys1−/− mice, these changes were limited to the fastest component of the inhibition, which was reduced (Fig. P1C). Thus, although dysbindin may have multiple roles, at the local circuit level, the dominance impact was a reduction in the fast-phasic inhibitory response.

Our work provides a model linking genetic risk factor for schizophrenia to a functional disruption in inhibition. This finding may help elucidate the neural basis for memory deficits and auditory-evoked EEG differences associated with genetic differences in dysbindin as well as schizophrenia. Recent work has shown that hippocampal γ-activity correlates with working memory performance. Additionally, the loss of fast inhibition reduces the ability of neuronal circuits to oscillate at high frequencies (Fig. P1 D and E), because the neurons must be repolarized (i.e., inhibited after being excited) quickly to participate in high-frequency γ-activity that can be recorded clinically with EEG.

Genetic differences in dysbindin-1 associated with symptoms of schizophrenia are relatively rare, but reduced expression of dysbindin is found in a large proportion of postmortem tissue from subjects with schizophrenia. Additionally, reduction in PV levels is common to schizophrenia and was also replicated in our mice. Thus, both dysbindin-1 dysregulation and inhibitory dysfunction are potential common disease mechanisms. Our data suggest that both abnormalities are functionally linked. Consistent with this view, reduced dysbindin-1 expression is also implicated in NMDA receptor dysfunction as a part of the excitatory pathway, which activates the PV cells (5), suggesting that the reduced NMDA receptor function hypothesis may link dysbindin-1 abnormalities and GABAergic dysfunction. These findings provide a framework in which these hypotheses can be further tested, and they strongly support the GABAergic dysfunction hypothesis of schizophrenia.