Dysbindin-1 Regulates Glutamatergic Synaptic Transmission in Memory-Related Cortical Networks

Jentsch, J.D.1,*

1Departments of Psychology and Psychiatry & Biobehavioral Sciences, University of California, Los Angeles 90095 USA
jentsch@psych.ucla.edu

Introduction

Dtnbtp1, the gene encoding dystrobrevin-binding-protein-1 (or dysbindin-1), has been implicated as a candidate risk gene for schizophrenia, by both linkage and association studies [1-3]. Furthermore, dysbindin-1 transcript and protein has been reported to be decreased in post mortem brain from schizophrenia patients, indicating that reduced expression of the molecule is implicated in disease pathophysiology [4-6]. These studies, utilizing a mouse model bearing a null mutation of the gene encoding dysbindin-1 [7], aimed to delineate the synaptic, systems and cognitive phenotypes causally linked to reduced expression of this protein.

Methods

Sdy mice, that carry a null mutation in the dtnbp1 gene, were subjects of study; all mice were on the C57Bl6 background. Behavioral studies involved the use of delayed non-match-to-position testing [8-9], contextual fear learning and novel object recognition tests. High field small animal magnetic resonance imaging at 7 Tesla, coupled with manganese-induced contrast enhancement, was employed [10]. Whole cell recordings from prefrontal cortical neurons were performed in cortical slices maintained in vitro [8-9].

Results and Discussion

Behavioral studies implicate patterns of dysfunction in memory-related circuits, including deficits in working memory maintenance and contextual and recognition memory, in mice with partial or complete loss of expression of dysbindin-1. In vivo neuroimaging demonstrated that these mnemonic deficits were associated with systems level dysfunction in the hippocampus, thalamus and dopaminergic circuitry. At the cellular and network levels, reduced or depleted expression of dysbindin-1 produced alterations in both pre- and post-synaptic aspects of glutamatergic transmission, including compromised glutamate release during high-frequency discharge and dramatically reduced NMDA receptor-mediated currents.

These results indicate that a variety of pathophysiological mechanisms often reported in schizophrenia – including glutamtergic NMDA and dopaminergic abnormalities – leading to cognitive/memory impairment can be explained, in part, by compromised expression of dysbindin-1. On-going studies are exploring the molecular mechanisms by which cascade failures in synaptic transmission occur after loss of dysbindin-1.
References