Altered axonal targeting and short-term plasticity in the hippocampus of Disc1 mutant mice


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Author Summary

There is accumulating evidence that rare mutational events constitute major causative factors in psychiatric disorders (1). Such rare mutations facilitated the discovery of a number of psychiatric disorder susceptibility genes. Here, we used a mouse model to investigate a mutation that disrupts the DISC1 gene in individuals with schizophrenia and mood disorders in a large family (2). We found that alterations in processing of neuronal information as well as anatomical structure underlie the influence of this mutation on how neurons connect and communicate with each other. These findings may explain the likely effects on disease susceptibility.

Mutations that predispose to mental illness likely disrupt the formation of neuronal circuits, both locally and at long distances. Such disruptions, in turn, likely underlie disease symptoms and predict their severity. Analysis of carefully designed animal models of disease-predisposing mutations holds great promise for discovering faulty circuits and the mechanisms by which they falter (3). Accordingly, we looked at a mouse strain that carries a mutation in Disc1 that corresponds to the mutation identified in humans (4). We focused on the hippocampus, a curved, elongated ridge-like structure of the brain that is involved in forming, storing, and processing memory. The Disc1 gene is expressed at high levels in one particular area of the hippocampus called the dentate gyrus (DG), a region that has been implicated in schizophrenia (5). Neurons in DG, also known as granule cells (GCs), receive sensory information from the cortex (the part of the brain most associated with thought, language, and consciousness) and relay it to a neighboring region of the brain called CA3. Axons of GCs, also known as mossy fibers (MFs), form synapses with neurons in the CA3 region and regulate their activity. Precise topography and remarkable moment to moment processing of neuronal information, also known as short-term synaptic plasticity, are key features of these synapses and ensure accurate relay and integration of sensory information. We found that the mutation in the Disc1 gene disrupts both of these features, thus affecting information transfer within this neural circuit. Specifically, we found that axons of mutant GCs are mistargeted outside the normal projection areas of the MFs (Fig. P1A). In addition, we showed that a form of short-term plasticity characteristic of MF synapses is adversely affected by the Disc1 mutation at normal GC firing rates. Additional data indicate that the mutation impairs information processing but not long-term storage (Fig. P1B).

How does the mutation in the Disc1 gene disrupt this circuit? Although the entire picture is not yet complete, our analysis does suggest a mechanism for one part: the observed axonal alterations. We show that the mutation results in decreased protein levels and enzymatic activity of phosphodiesterase 4 (PDE4), an enzyme involved in the breakdown of cAMP, a cyclic nucleotide of adenosine that acts as a second messenger in the regulation of various cellular processes. We show that altered cAMP levels, in turn, interfere with production of proteins that help steer the axons to their appropriate targets. In addition to these transcriptional effects, increases in cAMP levels may also affect the behavior of the tips of the developing axons (growth cones) in response to external repulsive or attractive cues.

To confirm that MF mistargeting is indeed because of increased cAMP levels, we first established that axonal mistargeting is recapitulated in cultured neurons and then investigated if manipulating cAMP levels can reverse it. Neurons from mutant mice were first assessed for their ability to respond to repulsive cues by using a stripe assay, where cultured neurons are challenged with alternating stripes of a repulsive molecule and allowed to either enter or avoid such stripes. Most WT axons were strongly repelled from entering the stripes. By contrast,


The authors declare no conflict of interest.

This Direct Submission article had a prearranged editor.

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See full research article on page E1349 of www.pnas.org.

Cite this Author Summary as: PNAS 10.1073/pnas.1114131108.
mutant axons displayed significantly reduced repulsion. Rapidly reducing cAMP levels in culture (through a drug treatment) reversed the repulsion in mutant neurons to WT levels, revealing that increased cAMP levels were responsible for the mutant effects.

Although the biology of DISC1 is being interrogated with a variety of approaches, our results represent a demonstration of how the pathogenic Disc1 mutation affects the fine structure and dynamic function of neural circuits. In that respect, our results tie together several emerging ideas about the pathophysiology of schizophrenia. Notably, our results support the notion that modest disturbances of neuronal connectivity and accompanying deficits in short-term synaptic dynamics may be a general, key feature of genetic mutations predisposing individuals to the disease.

Knowledge acquired from the Disc1 model regarding the structure and function of neural circuits can inspire development of new therapeutic targets regardless of genetic etiology, focusing on restoring abnormalities in biochemical pathways (such as cAMP signaling) or dynamic synaptic processes.