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PSYCHIATRIC DISORDERS

The dangers of adult-born neuron defects

> This important observation suggests that rapamycin can reverse DISC1 knockdown-induced behavioural phenotypes even in the presence of enduring structural abnormalities

The role of defects in adult-born neurons in schizophrenia and in other psychiatric conditions that are often classed as neurodevelopmental disorders remains unclear. However, a study in mice now shows that the knockdown of disrupted in schizophrenia 1 (DISC1) specifically in adult-born dentate gyrus (DG) neurons results in cognitive and other behavioural deficits, suggesting that abnormalities in such neurons may influence the phenotypes of these disorders.

DISC1 has been linked to schizophrenia and to some other psychiatric disorders that may have a neurodevelopment basis, and various *Disc1*-mutant animal models show abnormal nervous system and behavioural phenotypes. To knockdown DISC1 levels in newly born DG neurons in adult mice, the authors injected a retrovirus expressing a *Disc1*-targeted short hairpin RNA into the hilar region of the hippocampus. This induced defects in dendritic morphology, axonal targeting and cell positioning in these cells.

DISC1 knockdown impaired learning in mice in the object–place recognition task; increased immobility in the forced swim test, which is considered to be a depression-like behaviour; and induced anxiety-like behaviour in the elevated plus maze. Thus, defects in adult-born neurons alone can alter cognitive and affective behaviour in mice.

Rapamycin inhibits mammalian target of rapamycin (mTOR) signalling and has previously been shown to prevent DISC1 knockdown-induced morphological defects in adult-born neurons. In the new study, intraperitoneal administration of rapamycin 5 days after DISC1 knockdown prevented the development of dendritic and cell-positioning defects in adult-born DG neurons. It also prevented learning impairments and depression- and anxiety-like behaviours.

When the authors administered rapamycin 2 weeks after DISC1 knockdown in DG neurons, it failed to reverse the dendritic and cell-positioning defects. However, it did rescue the abnormal mTOR signalling in DG neurons and, strikingly, the behavioural deficits. This important observation suggests that rapamycin can reverse DISC1 knockdown-induced behavioural phenotypes even in the presence of enduring structural abnormalities.

This study shows that abnormalities in adult-born neurons can cause cognitive and affective changes in mice, which implies that defects in such neurons might have a role in the enduring phenotypes that are associated with schizophrenia and related disorders. It also shows that the behavioural effects of certain structural deficits may be overcome through pharmacological intervention without reversing the structural deficits themselves.

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ORIGINAL RESEARCH PAPER Zhou, M. *et al.* mTOR inhibition ameliorates cognitive and affective deficits caused by Disc1 knockdown in adult-born dentate granule neurons. *Neuron* **77**, 647–654 (2013)

FURTHER READING Brandon, N. J. & Sawa, A. Linking neurodevelopmental and synaptic theories of mental ill ness through DISC1. *Nature Rev. Neurosci.* **12**, 707–722 (2011)