PSYCHIATRIC DISORDERS

Simulating schizophrenia

Modelling human psychiatric disorders in animals is challenging, in part because the mechanisms that underlie such disorders are complex, and often interrelated. This makes the generation of animal models that reproduce all the characteristics of a particular disease difficult, if not impossible. Nevertheless, Kellendonk and colleagues from the Kandel group, writing in *Neuron*, now describe an elegant new mouse model of schizophrenia that sheds light on the pathophysiology of this disorder and could aid in the development of new drugs.

Overactivity of dopamine 2 (D_2) receptors has long been implicated in the pathophysiology of schizophrenia. Indeed, all effective anti-psychotic drugs block D_2 receptors and, in particular, improve the positive symptoms of the disease, such as hallucinations and delusions. However, these drugs typically only have modest beneficial effects on cognitive impairments associated with schizophrenia, such as deficits in working memory, and it has been more difficult to determine whether D_2 receptors have any role in these symptoms.

To investigate this issue, Kellendonk and co-workers developed transgenic mice in which overexpression of D_2 receptors was restricted to the striatum, as increased activity of D_2 receptors in this area has been implicated in schizophrenia. Importantly, expression of the D_2 receptor transgene could be 'switched off' by oral administration of the antibiotic doxycycline.

Although the general behaviour of the mice overexpressing D_2 receptors was unaffected, standard tests of working memory and behavioural flexibility showed that the mice had cognitive impairments similar to those experienced by people with schizophrenia. The deficits in working memory remained after administration of doxycycline to the mice, suggesting that it is excess D_2 receptor activity during development, rather than continued overexpression, that is important in causing these deficits. The authors also note that this might explain why treatment with current anti-psychotic drugs does not significantly affect cognitive deficits in schizophrenic patients: such treatment is too late to reverse the underlying physiological alterations.

Finally, Kellendonk *et al.* investigated the effects of striatal overexpression of D_2 receptors in the prefrontal cortex (PFC), the main structure associated with working memory, and noted changes in dopamine levels, rates of dopamine turnover and activation of D_1 receptors in the PFC, all of which are crucial in working memory. The authors therefore suggest that it will be interesting to assess whether D_1 receptor blockade in the PFC would reverse the cognitive deficits in their D_2 transgenic mice, potentially highlighting an avenue for the development of improved antipsychotic drugs. And in general, this model could prove useful in predicting the effects of any potential antipsychotic agent on the cognitive impairments associated with schizophrenia in humans.

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ORIGINAL RESEARCH PAPER Kellendonk, C. *et al.* Transient and selective overexpression of dopamine D2 receptors in the striatum causes persistent abnormalities in prefrontal cortex functioning. *Neuron* **49**, 603–615 (2006)