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An up for Down

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Inhibiting GABA-mediated inhibition improves learning and memory in a mouse model of Down syndrome.

It is difficult to be positive when you are surrounded by negativity. Cognitive impairment associated with Down syndrome may be caused by an imbalance in excitatory and inhibitory synapses that leads to excessive GABA-mediated inhibition. Now Fernandez *et al.* report improved cognition in a mouse model of Down syndrome following treatment with GABAA receptor antagonists in a recent article in *Nature Neuroscience*.

Ts65Dn mice model the pathophysiology of Down syndrome, which is caused by an extra copy (trisomy) of human chromosome 21. Ts65Dn mice have trisomy of a section of mouse chromosome 16, which is most similar to human chromosome 21. Similar to people with Down syndrome, Ts65Dn mice show delayed development, impaired cognition and age-related neurodegeneration. Ts65Dn mice show impaired induction of hippocampal long-term potentiation (LTP), which is important in learning and memory. The authors hypothesized that reduction of GABA-mediated inhibition would normalize learning and memory in Down syndrome.

The authors tested adult mice in the novel object recognition task, which tests object memory. Wild-type mice explored new objects more than familiar ones. Ts65Dn mice did not prefer new objects to familiar ones, suggesting that their object memories are impaired. However, two-week treatment with the GABAA receptor antagonist picrotoxin rescued novel object discrimination in Ts65Dn mice.

In Ts65Dn mice, GABAA receptor antagonists improved performance on the spontaneous alternation task, which tests spatial memory. After exploring one arm of a T-maze, wild-type mice tend to explore the other. However, Ts65Dn mice showed decreased arm alternation relative to wild-type mice, suggesting that Ts65Dn mice did not remember their previous location. In contrast, Ts65Dn mice treated with the GABAA receptor antagonist pentyleneetetrazole showed alternation comparable to wild-type mice, suggesting improved learning and memory.

GABAA receptor antagonist-mediated improvement in cognition persisted after treatment stopped. Two weeks after treatment, picrotoxin-treated Ts65Dn mice and wild-type mice explored new and familiar objects similarly. Two months after a 17-day treatment, Ts65Dn mice that consumed pentyleneetetrazole in milk were comparable to wild-type mice in novel object recognition.

Ts65Dn mice showed impaired LTP in the dentate gyrus relative to wild-type mice. Thirty days after pentyleneetetrazole treatment, Ts65Dn mice showed improved LTP, comparable to that of wild-

type mice, and sixty to ninety days after pentylentetrazole treatment, the improvement persisted, albeit at reduced levels.

Together, these data suggest that despite abnormal neuronal development in a mouse model of Down syndrome, restoring the balance between excitation and inhibition rescues learning in the adult. GABA

receptor antagonists may improve cognition in people with Down syndrome. However, these drugs can cause seizures, so their dosage will need to be carefully titrated.

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1. Fernandez, F. *et al.* Pharmacotherapy for cognitive impairment in a mouse model of Down syndrome. *Nature Neuroscience* **10**, 411–413 (2007). | [Article](#) |