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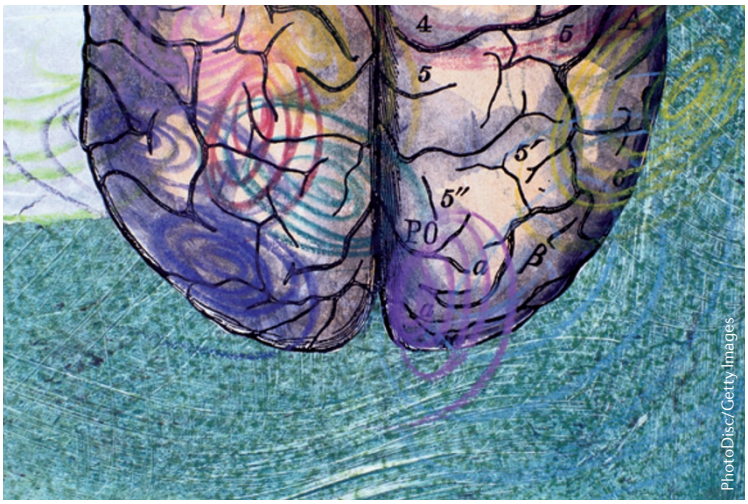
NEUROLOGICAL DISORDERS

Targeting translation in autism

Autism spectrum disorders (ASDs) are complex neurodevelopmental conditions characterized by communication deficits, irritability, repetitive behaviours and restricted interests. Although the precise aetiology of ASDs is poorly understood, hyperconnectivity of neuronal circuits owing to increased synthesis of synaptic proteins is thought to be involved. Now, writing in *Nature*, Gkogkas and colleagues show that deleting the gene encoding the translational repressor eukaryotic translation initiation factor 4E (eIF4E)-binding protein 2 (4EBP2) in mice results in increased translation of neuroligins, which are associated with synaptic dysfunction and autistic-like behaviours. Moreover, pharmacological inhibition of eIF4E activity or small interfering RNA (siRNA)-mediated knockdown of neuroligin 1 reverses these abnormalities, identifying novel potential targets for the treatment of ASDs.



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The eIF4F complex — which is composed of the cap-binding protein eIF4E, the RNA helicase eIF4A and the modular scaffolding protein eIF4G — is required for translation initiation of most mRNAs. eIF4F complex activity is regulated by 4EBPs, which repress eIF4E and disrupt complex formation. Recent studies have implicated a role for dysregulated eIF4E-dependent translation in ASD, so the authors set out to further investigate this hypothesis.

First, they knocked out 4EBP2 — the major 4EBP in the mammalian brain that has an important role in long-lasting synaptic plasticity, learning and memory — in mice, which would mimic the effects of eIF4E upregulation. These mice exhibited autistic-like behaviour, displaying social interaction deficits, altered communication and repetitive behaviours.

Next, the authors investigated the effects of dysregulated eIF4E activity on mRNA translation. They performed polysome profiling to measure the translation of 24 mRNAs coding for proteins known to be associated with ASD in hippocampal lysates from 4EBP2-knockout mice and mice overexpressing eIF4E. This revealed that there was increased translation of mRNA for neuroligins 1–4 (adhesion proteins that mediate neuronal synapse formation and are involved in controlling the balance of excitatory and inhibitory synapses) in these mouse models compared to wild-type control mice. Indeed, there were no changes in mRNA levels, whereas protein levels of all four neuroligins were increased. In addition, an increased ratio of excitatory to inhibitory (E/I) synaptic inputs was observed in the mice lacking 4EBP2, an observation that has previously been proposed to cause ASD.

Next, to investigate whether the ASD-like phenotype could be rescued pharmacologically, the authors used the selective small-molecule inhibitor 4EGI-1 — a hydrazone compound that prevents eIF4E binding to eIF4G during eIF4F complex formation. In hippocampal slices from 4EBP2-knockout mice, 4EGI-1 reduced neuroligin protein levels and restored the E/I balance. In addition, intracerebroventricular infusion of mice with 4EGI-1 for 5 days rescued the social behaviour deficits. Similar beneficial effects were observed following siRNA-mediated knockdown of neuroligin 1.

In summary, these findings support a role for dysregulated eIF4E-mediated translation in the development of ASDs and highlight novel therapeutic approaches for reversing ASD symptoms.

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ORIGINAL RESEARCH PAPER Gkogkas, C. G. *et al.* Autism-related deficits via dysregulated eIF4E-dependent translational control. *Nature* 21 Nov 2012 (doi:10.1038/nature11628)