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NEURODEVELOPMENTAL DISORDERS

Overproducing autism

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It has been proposed that increased protein synthesis caused by dysregulated translational control may be an important mechanism underlying autism. Two new studies support this proposal by showing that, in mice, increased eukaryotic translation initiation factor 4E (eIF4E)-dependent translation causes autism-related behavioural and synaptic deficits.

eIF4E binds to the 5′ methylguanosine cap present on many mRNAs, allowing recruitment of ribosomes to the mRNAs and translation. Several studies have suggested a link between eIF4E and autism.

Santini *et al.* studied this link in eIF4E-overexpressing transgenic mice (eIF4E mice) and showed that increased brain eIF4E levels in these mice were associated with increased protein synthesis, indicating a rise in eIF4E-dependent translation.

The characteristics of autism include social interaction deficits and repetitive behaviour. In line with these behaviours, eIF4E mice showed repetitive digging in a marble-burying task and, unlike wild-type mice, no preference for a strange mouse over a novel object when presented with both simultaneously.

eIF4E mice also showed altered synaptic transmission in the prefrontal cortex and abnormal synaptic plasticity in the striatum and hippocampus — brain regions that are implicated in behavioural deficits in autism. Furthermore, eIF4E mice treated with 4EGI-1, an eIF4E inhibitor, showed improvements in the behavioural deficits and normal synaptic plasticity in the striatum.

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These results indicate that increased eIF4E-dependent translation causes an autism-like condition in mice.

Gkogkas *et al.* studied mice in which the eIF4E binding protein 2 (4E-BP2) gene (*Eif4ebp2*) was knocked out. The absence of 4E-BP2 would be predicted to promote eIF4E activity, as 4E-BP2 inhibits eIF4E activity.

Like eIF4E mice, *Eif4ebp2*$^{-/-}$ mice exhibited repetitive digging, social interaction deficits and changes in hippocampal synaptic transmission and plasticity, altering the excitation/inhibition (E/I) ratio. In addition, out of 24 mRNAs encoding proteins previously linked to autism, only four transcripts, encoding neuroligins (NLGNs), showed increased translation in the *Eif4ebp2*$^{-/-}$ hippocampus, suggesting that altered eIF4E-dependent translation upregulates only a subset of proteins.

Knockdown of NLGN1 selectively normalized excitatory transmission in *Eif4ebp2*$^{-/-}$ hippocampal slices, normalizing the E/I ratio, and partially reversed the social behavioural deficits. Interestingly, NLGN2 knockdown specifically normalized inhibitory synaptic transmission, failing to normalize the E/I ratio, and augmented the behaviours. Thus, altered E/I balance — a feature of several other mouse models of autism — seems to underlie the autism-like behaviours in *Eif4ebp2*$^{-/-}$ mice.

Together, the results of these studies suggest that dysregulated eIF4E translational control induces autism-like behaviours and synaptic transmission and plasticity abnormalities through upregulating NLGNs.

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ORIGINAL RESEARCH PAPERS Santini, E. *et al.* Exaggerated translation causes synaptic and behavioural aberrations associated with autism. *Nature* 23 Dec 2012 (doi:10.1038/nature11782) | Gkogkas, C. G. *et al.* Autism-related deficits via dysregulated eIF4E-dependent translational control. *Nature* 21 Nov 2012 (doi:10.1038/nature11628)