NEURODEVELOPMENTAL DISORDERS

A fragile synaptic balance

A number of specific gene mutations are associated with intellectual disability and autism, providing hope that understanding common downstream effects might shed light on the pathophysiology of autism spectrum disorders. Bear and colleagues now show that mutations in fragile X mental retardation 1 (*FMR1*) and tuberous sclerosis 2 (*TSC2*), which are associated with similar behavioural impairments, have opposing effects on metabotropic glutamate receptor 5 (mGluR5) function and synaptic protein synthesis.

In fragile X syndrome (FXS), silencing of *FMR1* increases mRNA translation downstream of mGluR5 activation, leading to increased long-term depression (LTD) at mGluR5-expressing synapses. The mutations in *TSC1* or *TSC2* that cause tuberous sclerosis are also thought to influence mRNA translation and synaptic function, suggesting that similar mechanisms might be involved. The authors were therefore surprised to observe that mGluR5-LTD in the hippocampal CA1 area was suppressed, rather than increased, in a mouse model of tuberous sclerosis ($Tsc2^{+/-}$ mice) and that there was a corresponding decrease in the synthesis of LTD-related proteins.

In animal models of FXS, reducing mGluR5 signalling can correct the abnormalities in protein synthesis and LTD. Here the authors found that a positive allosteric modulator (PAM) that boosts mGluR5 signalling returned both protein synthesis and LTD to wild-type levels in $Tsc2^{+/-}$ mice. Furthermore, the mGluR5 PAM was able to restore performance in a context discrimination task in which $Tsc2^{+/-}$ mice were impaired.

These results suggest that *FMR1* and *TSC2* mutations have opposing effects on protein synthesis and mGluR5 function. Indeed, their effects appear to cancel each other: the authors found that mGluR-LTD, protein synthesis and context discrimination were normal in mice carrying both mutations.

The behavioural characteristics of FXS and tuberous sclerosis are similar, suggesting that mutations that shift the balance of mGluR5 signalling in either direction have similar effects on cognitive function. The findings confirm the restoration of synaptic function to be a key target in the development of therapeutic strategies for autism spectrum disorders; however, they also suggest that such treatments will need to take into account the specific deficits present in each case.

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> “These results suggest that *FMR1* and *TSC2* mutations have opposing effects on protein synthesis and mGluR5 function”

ORIGINAL RESEARCH PAPER Auerbach, B. D., Osterweil, E. K. & Bear, M. F. Mutations causing syndromic autism define an axis of synaptic pathophysiology. *Nature* **480**, 63–68 (2011)

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