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NEURODEVELOPMENTAL DISORDERS

Targeting translation

The genetic heterogeneity associated with autism spectrum disorder (ASD), a condition with altered social interactions, has complicated the search for treatments. To circumvent this issue, some recent work on developing therapeutics for ASD has focused on oxytocin and vasopressin, which are neuropeptides that regulate features of mammalian social behaviour. However, whether genetic risk factors associated with ASD modify oxytocin and/or vasopressin signalling was unclear. Hörnberg et al. now show that, in mice, loss of the autism risk gene *Nlgn3*, which encodes a synaptic adhesion molecule, impairs oxytocin signalling and alters social behaviour.

To model social recognition (which is commonly altered in individuals with ASD), the authors assessed juvenile mice in a five-trial social habituation–recognition task, observing that the behavioural response to social novelty was altered in *Nlgn3* knock out ($Nlgn3^{KO}$) mice compared with wild-type mice. Dopaminergic neurons in the ventral tegmental area (VTA DA neurons) are known to be involved in this behavioural response, which was restored in $Nlgn3^{KO}$ mice by selectively restoring *Nlgn3* expression in dopaminergic neurons. As social recognition was also altered in wild-type mice injected intraperitoneally prior to assessment with an oxytocin receptor antagonist, social recognition in this assay is dependent on oxytocin signalling.

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Previous work indicated that during the behavioural response to social novelty, oxytocin from axons originating in hypothalamic nuclei increases the firing of VTA DA neurons projecting into the nucleus accumbens. Investigating the link between *Nlgn3* and oxytocin signalling the authors found that, compared with wild-type mice, baseline firing of VTA DA neurons was reduced in $Nlgn3^{KO}$ mice. Furthermore, as the addition of oxytocin increased firing in wild-type but not $Nlgn3^{KO}$ mice, *Nlgn3* appears to be required for oxytocin responses in the VTA.

To identify molecular differences between VTA DA neurons from $Nlgn3^{KO}$ mice and those from wild-type mice, the authors analysed VTA tissue using shot-gun proteomics, observing that the expression of proteins involved in translation was altered in $Nlgn3^{KO}$ mice. Interestingly, in mice exposed to handling, translation was increased in VTA DA neurons of acute brain slices from $Nlgn3^{KO}$ mice compared to wild-type controls. MAP kinase-interacting kinases (MNKs) regulate mRNA translation and oral administration of the novel MNK inhibitor ETC-168, which penetrated the brain, reduced phosphorylation of a MNK-targeted translation initiation factor in the VTA of wild-type mice. The inhibition of MNKs is known to improve a behavioural phenotype in mice in which *Fmr1* (encoding synaptic functional regulator FMR1) has been knocked out and ETC-168 also reduced a cognitive rigidity phenotype in these mice. These data indicate that ETC-168 can modify both translation and cognitive behaviour in mice, and the authors asked if it could rescue the changes they had seen in $Nlgn3^{KO}$ mice.

Indeed, the authors observed an increase in cytoplasmic ribosomal components in $Nlgn3^{KO}$ mice compared with controls, which was abolished by oral treatment with ETC-168. In addition, in acute brain slices from $Nlgn3^{KO}$ mice treated with ETC-168, translation was reduced compared to that in slices from vehicle-treated $Nlgn3^{KO}$ mice and it was similar to the level of translation observed in slices from wild-type vehicle-treated mice. Furthermore, treatment of $Nlgn3^{KO}$ mice with ETC-168 restored their ability to undergo an oxytocin-induced increase in the firing frequency of VTA DA neurons as well as social novelty responses. Thus, in $Nlgn3^{KO}$ mice, inhibiting MNK appears to modify translation to rescue oxytocin signalling and social behaviour.

The authors conclude that their study links a genetic risk factor of ASD to the regulation of translation, oxytocin signalling and social novelty responses. Moreover, the work implicates the newly generated MNK inhibitor as a putative therapeutic strategy for neurodevelopmental conditions underscored by alterations in translation.

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This article originally appeared in *Nat. Rev. Neurosci.* (https://doi.org/10.1038/s41583-020-0368-1)

ORIGINAL ARTICLE Hörnberg, H. et al. Rescue of oxytocin response and social behaviour in a mouse model of autism. *Nature* **584**, 252–256 (2020)