NEWS

Modified Alzheimer's drug may treat some forms of autism

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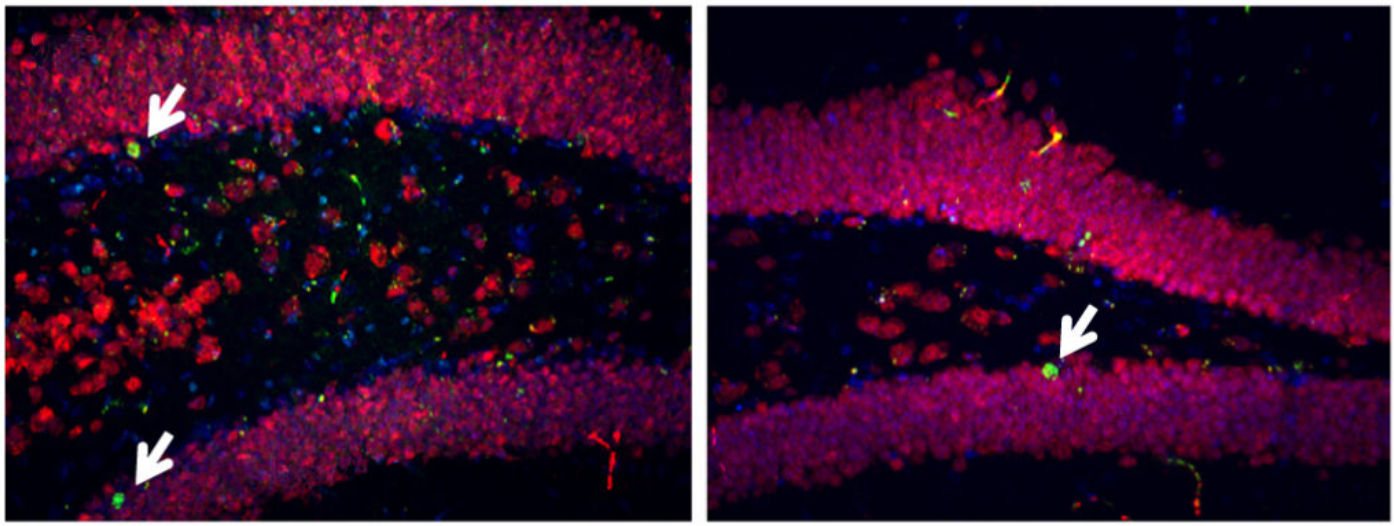

A fusion of two existing drugs alleviates autism-like features in a mouse model of the condition, according to a new study[1].

The fusion drug, called NitroSynapsin, boosts social interest and alleviates some **repetitive behaviors** in mice missing one copy of the autism candidate gene **MEF2C**.

The drug appears to work by tamping down overactive brain signaling; a signaling imbalance that leads to excess neuronal activity **may be a unifying feature of autism**.

"We have a decent chance of treating many different forms of autism," says lead researcher **Stuart Lipton**, co-director of the Neuroscience Translational Center at the Scripps Research Institute in La Jolla, California.

Lipton's team has unpublished data showing that the drug also eases autism features in mouse

models of tuberous sclerosis and Rett syndrome, conditions related to autism.

It's too soon to say whether the drug is safe and effective in people with these conditions, but the results are promising, experts say.

"It's welcome to add to the repertoire of compounds that might eventually offer some benefit to people with autism," says **Grainne McAlonan**, deputy head of forensic and neurodevelopmental science at King's College London.

Drug duet:

NitroSynapsin is a modified form of memantine, a drug that has been used for years to treat dementia and Alzheimer's disease. Researchers considered memantine as a possible autism treatment because it lowers the activity of so-called NMDA receptors. These receptors respond to the chemical messenger glutamate and mediate excitatory brain signals.

Clinical trials of memantine **found some improvements** in people with autism, but no more than with a placebo[2]. Still, Lipton saw NMDA receptors as a good target for treating autism and developed NitroSynapsin. "[Memantine] does a little good, but we need something more powerful," he says.

His team fused a part of memantine with part of another drug, nitroglycerin, which also regulates the activity of NMDA receptors. The memantine component guides nitroglycerin to the NMDA receptors.

However, turning up memantine's potency might increase its side effects, notes **Stephen Moss**, professor of neuroscience at Tufts University in Boston. For example, the use of ketamine, a more powerful version of memantine, sometimes leads to drug abuse and addiction, he says.

"If their compound is anything like ketamine, which works the same way, then it could have some very dubious side effects," he says.

Memory gap:

Lipton's team focused on MEF2C mutations, as they are known to enhance brain signals, making them a good target for the drug. Children with mutations in MEF2C have a syndrome characterized by intellectual disability, **epilepsy** and features of autism. MEF2C also regulates the expression of other autism candidate genes[2].

The mutant mice have some repetitive behaviors, such as clasping their hind limbs or forelimbs together and repeatedly dipping their heads into holes in a board. They also have memory problems and show no preference for investigating a mouse over an object — a sign of social

problems.

Mice given NitroSynapsin for three months show improvements in memory and display the typical preference for a mouse over an object. They also stop obsessively poking their nose into the board, but continue to clasp their limbs.

The mutants have fewer neurons than controls in the frontal cortex and the **hippocampus**, a brain region that regulates memory, the researchers found. They also have a lower ratio of neurons that dampen brain activity to those that activate it in the hippocampus.

NitroSynapsin restores both the neuron numbers and the neuron ratio to normal levels. The findings appeared 14 November in *Nature Communications*.

Lipton and his team have generated neurons from the skin cells of children who carry a mutation in MEF2C. NitroSynapsin normalizes signaling in these neurons, according to preliminary data. The next step, Lipton says, is to try the drug in clinical trials in people with MEF2C mutations.

REFERENCES:

1. Tu S. *et al. Nat. Commun.* **8**, 1488 (2017) **PubMed**
2. Parikshak N.N. *et al. Cell* **155**, 1008-1021 (2013) **PubMed**