Neuroscientists find that two rare autism-related disorders are caused by opposing malfunctions in the brain

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(Medical Xpress) -- Most cases of autism are not caused by a single genetic mutation. However, several disorders with autism-like symptoms, including the rare Fragile X syndrome, can be traced to a specific mutation. Several years ago, MIT neuroscientist Mark Bear discovered that this mutation leads to overproduction of proteins found in brain synapses -- the connections between neurons that allow them to communicate with each other.

In a paper published today in *Nature*, Bear and colleagues have now shown that tuberous sclerosis, another rare disease characterized by autism and mental retardation, is caused by the opposite malfunction — too little synthesis of those synaptic proteins.

Though the findings might seem counterintuitive, they fit into the theory that autism can be caused by a wide range of brain-synapse glitches, Bear says. “The general concept is that appropriate brain function occurs within a very narrow physiological range that is tightly maintained,” he says. “If you exceed that range in either direction, you have an impairment that can manifest as this constellation of symptoms, which very frequently go together — autism spectrum disorder, intellectual disability and epilepsy.”

Furthermore, the study suggests that any potential drugs developed to treat the cellular origins of autism would need to be carefully matched to

the patient to ensure they do more good than harm. Drugs developed to treat Fragile X syndrome have shown encouraging results in human studies and are currently in Phase III clinical trials.

Making connections

Bear, the Picower Professor of Neuroscience and a member of MIT's Picower Institute for Learning and Memory, did not set out to study autism or Fragile X syndrome, but ended up discovering how Fragile X develops through his studies of a receptor found on the surface of neurons.

That receptor, known as mGluR5, plays an important role in transmitting signals between two neurons at a synapse (known as the presynaptic and postsynaptic neurons). When the presynaptic cell releases a neurotransmitter called glutamate, it binds to mGluR5 on the postsynaptic neuron, triggering synthesis of new synaptic proteins. Fragile X protein (FMRP) acts as a brake on this protein synthesis. "The appropriate level of protein synthesis is generated by a balance between stimulation by mGluR5 and repression by FMRP," Bear says.

When FMRP is lost, there is too much protein synthesis, which leads to the symptoms seen in Fragile X syndrome: learning disabilities, autistic behavior and seizures. Bear and others have since shown that blocking mGluR5 in mice can reverse those symptoms.

After making the connection between Fragile X and mGluR5, Bear and his colleagues started to wonder if mGluR5 overactivity might also cause other single-gene syndromes that produce autism symptoms. They began their investigation with tuberous sclerosis (TSC).

The researchers, including co-authors Benjamin Auerbach, a graduate student in brain and cognitive sciences, and research scientist Emily

Osterweil, felt confident in their hypothesis that they would see a similar synaptic defect in TSC as they had seen in Fragile X. In fact, when they submitted their application for funding for the study, “our reviewers thought we were being too conservative, because it seemed to them that the answer was so obvious, it was hardly worth doing the experiment,” Bear recalls.

However, the team found the exact opposite of what they and the reviewers had expected. The two diseases “appear to be mirror images of each other,” Bear says. In mice with TSC, synapses have too little protein synthesis — so instead of improving when treated with a drug that inhibits mGluR5, the animals respond to a drug that stimulates it.

Tailored treatments

The findings show that not all cases of autism spectrum disorder will respond to the same kind of treatment, Bear says. “This study identified one functional axis, and it will be important to know where a patient lies on this axis to devise the therapy that will be effective,” he says. “If you have a disorder of too little protein synthesis, you don’t want to inhibit the neurotransmitter receptor that stimulates protein synthesis, and vice versa.”

This should not be surprising, he says, pointing out that psychiatric-drug development has encountered the same difficulties, because disorders such as bipolar disorder and schizophrenia have such varied origins. In the case of autism, researchers hope that identifying the root causes of single-gene disorders can help them figure out how to treat other forms of autism that may have similar origins.

“We have a huge advantage of really getting down to what actually is wrong in the brain in these diseases,” Bear says. “Of course what we’d like to do is be able to go from these rare known causes of autism, which

may account for at most 10 percent of cases of autism, into idiopathic autism — autism of unknown cause — and try to have some hope of selecting the right therapy for those individuals."

There are currently no good tests for which genetic markers a particular autistic patient may have, but if drugs that inhibit and/or stimulate mGluR5 are approved, scientists may be able to identify which autistic patients respond to which drugs, and then try to identify a biomarker in those patients that could be used for future diagnostic tests.

Bear and his colleagues are now studying other single-gene disorders, including Angelman syndrome and Rett syndrome, to see if they also affect mGluR5 activity. They are also trying to figure out, in more detail, the steps in the mGluR5/protein-synthesis pathway.

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