Novel mouse model for autism yields clues to a 50-year-old mystery

March 20 2012

Jeremy Veenstra-VanderWeele (left) and Randy Blakely pose at the entrance to the Vanderbilt Laboratory for Neurobehavior, where their studies in mice have revealed a clue to autism. Credit: Susan Urmy/Vanderbilt University

Early disruptions in serotonin signaling in the brain may contribute to autism spectrum disorder (ASD), and other "enduring effects on behavior," Vanderbilt University researchers report.

Serotonin is a brain chemical that carries signals across the synapse, or gap between nerve cells. The supply of serotonin is regulated by the serotonin transporter (SERT). In 2005, a team of Vanderbilt researchers led by Randy Blakely and James Sutcliffe identified rare genetic variations in children with ASD that disrupt SERT function.

In a new study published this week in the Proceedings of the National Academy of Sciences (*PNAS*), the researchers report the creation of a mouse model that expressed the most common of these variations.

The change is a very small one in biochemical terms, yet it appears to cause SERT in the brain to go into "overdrive" and restrict the availability of serotonin at synapses.

"The SERT protein in the brain of our mice appears to exhibit the exaggerated function and lack of regulation we saw using cell models," said Blakely, director of the Vanderbilt Silvio O. Conte Center for Neuroscience Research.

"Remarkably, these mice show changes in social behavior and communication from early life that may parallel aspects of ASD," noted first author Jeremy Veenstra-VanderWeele, assistant professor of Psychiatry, Pediatrics and Pharmacology.

The researchers conclude that a lack of serotonin during development may lead to long-standing changes in the way the brain is "wired."

In 1961, investigators at Yale discovered that as many as 30 percent of children with autism have elevated blood levels of serotonin, a finding described as "hyperserotonemia."

Since then, these findings have been replicated many times. Indeed, hyperserotonemia is the most consistently reported biochemical finding in autism, and is a highly inherited trait. Yet, the cause or significance of this "bio-marker" has remained shrouded in mystery.

Until now. In the current study, Veenstra-VanderWeele, Blakely and their colleagues showed that they could produce hyperserotonemia in mice that express a variant of a human SERT gene associated with

autism.

Because the genetic change makes the transporter more active, higher levels of serotonin accumulate in platelets and therefore in the bloodstream. In the brain, overactive transporters should have the opposite effect – lowering serotonin levels at the synapse and producing behavioral changes relevant to autism. That's exactly what the researchers observed.

Of course, no mouse model can completely explain or reproduce the human condition. Neither does a single genetic variation cause autism. Experts believe the wide spectrum of autistic behaviors represents a complex web of interactions between many genes and environmental factors.

But animal models are critical to exploring more deeply the basis for the developmental changes that are observed in ASD. The scientists are using these mice to explore how altered brain serotonin levels during development may produce long-lasting changes in behavior and impact the risk for autism.

Provided by Vanderbilt University Medical Center