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New clue to autism found inside brain cells

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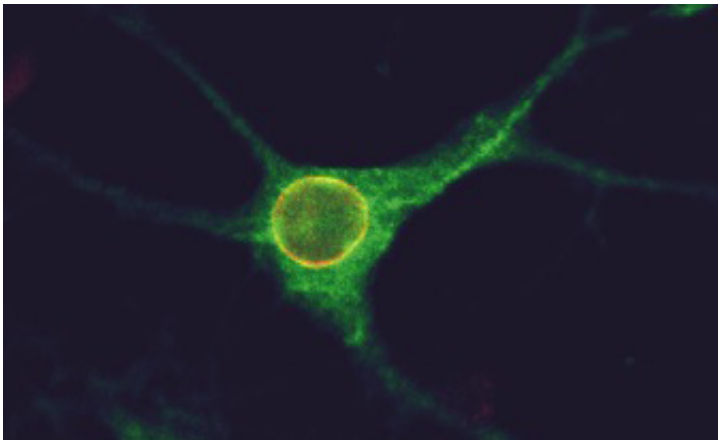

Learning, social interaction and other mental functions in people with autism may be affected by receptors inside brain cells, scientists at Washington University School of Medicine have learned. The type of receptor they studied glows green on the surface of this cell. Inside the cell it covers a membrane that is stained red. Credit: Yuh-Jiin I. Jong

The problems people with autism have with memory formation, higher-level thinking and social interactions may be partially attributable to the activity of receptors inside brain cells, researchers at Washington University School of Medicine in St. Louis have learned.

Scientists were already aware that the type of receptor in question was a potential contributor to these problems – when located on the surfaces of brain cells. Until now, though, the role of the same type of receptor located inside the cell had gone unrecognized. Such receptors inside cells

significantly outnumber the same type of receptors on the surface of cells.

The receptor under study, known as the mGlu5 receptor, becomes activated when it binds to the neurotransmitter glutamate, which is associated with learning and memory. This leads to chain reactions that convert the glutamate's signal into messages traveling inside the cell.

In the new study, scientists working with cells in a dish linked mGlu5 receptors inside cells to processes that turn down the volume at which brain cells talk to each other. These volume changes, essential for learning and memory, may become exaggerated in people with autism.

Pharmaceutical companies have developed therapeutic compounds to decrease signaling associated with the mGlu5 receptor, moderating its effects on brain cells' volume knobs. But the compounds were designed to target mGlu5 surface receptors. In light of the new findings, the scientists question if those drugs will reach the receptors inside cells.

"Our results suggest that to have the greatest therapeutic benefit, we may need to make sure we're blocking all of this type of receptor, both inside and on the surface of the cell," said senior investigator Karen O'Malley, PhD, professor of neurobiology.

The findings, published March 25 in *The Journal of Neuroscience*, also add a significant new dimension to basic brain cell function. Scientists have long assumed that brain cell receptors are only active on the surface of cells. The new study shows that receptors can be active inside cells, and their effects can be considerably different from the same receptors located on the cell surface.

"The traditional wisdom was that receptors inside the cell were either waiting to go to work on the surface or had just finished working there,"

said O'Malley. "But when we compared how much of the mGlu5 receptor was on the surface of cells to how much was inside it, we were seeing so much more receptor inside the cell – at least 50 percent, and in some cases as much as 90 percent – that we wondered if the interior receptors had separate functions."

In earlier studies, O'Malley and her collaborators showed that mGlu5 receptors on the cell surface sent completely different messages than the same receptors inside the cell.

The scientists knew that most autism studies were conducted with compounds that blocked mGlu5 receptors but could not get into the cell. To determine whether blocking inside receptors would have different effects, O'Malley collaborated with Yukitoshi Izumi, MD, PhD, research professor of psychiatry, and Charles F. Zorumski, MD, the Samuel B. Guze Professor and head of the Department of Psychiatry, who study cell-based models of learning and memory.

When the scientists examined these model systems using compounds that allowed them to activate only mGlu5 receptors within cells, they found that these receptors played a bigger role in turning down the volume of brain cell communications than did the cell surface receptors.

In the last few years, scientists have found that 20 or more types of brain cell receptors located on cell surfaces also are present at high levels inside cells, O'Malley noted.

"This should be a factor we consider when we design drugs to target brain cell receptors," she said. "Do we want to reach cell surface receptors, receptors inside the cell or both?"

More information: Purgert CA, Izumi Y, Jong Y-J I, Kumar V, Zorumski CF, O'Malley KL. Intracellular mGluR5 can mediate synaptic

plasticity in the hippocampus. The *Journal of Neuroscience*, March 25, 2014.

Provided by Washington University School of Medicine