Researchers uncover biochemical pathway by which harmful molecule may raise Alzheimer's risk

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A molecule implicated in Alzheimer's disease interferes with brain cells by making them unable to "recycle" the surface receptors that respond to incoming signals, researchers at UT Southwestern Medical Center have found.

The harmful molecule, called APOE4, is present in about one out of every six people, the researchers said. Those with the gene for APOE4 have up to 10 times the risk of developing Alzheimer's disease earlier in life than average.

The researchers discovered that APOE4 makes a nerve cell hold back the molecules that enables it to respond to other cells, thereby disabling a chemical process known to be important in learning. Their findings appear online this week in the Proceedings of the National Academy of Sciences.

"This is actually a fairly simple system," said Dr. Joachim Herz, director of the Center for Alzheimer's and Neurodegenerative Disease at UT Southwestern and senior author of the study. "For the first time, we see an uninterrupted biochemical pathway that links the surface of the brain cell to the dysfunction inside the cell, and specifically at the junction at which nerve cells communicate."

The research focused on a basic characteristic of nerve cells called

neurotransmission, in which they use chemicals to signal each other. When one nerve cell needs to "talk" to another, its tip sends out a chemical called a neurotransmitter. The surface of the second cell is studded with molecules called receptors, which fit specific neurotransmitters like a lock and key. When a neurotransmitter docks onto its receptor, the second cell responds.

A cell can fine-tune its sensitivity by removing receptors from its surface. To do this, the cell engulfs the receptors to its interior, taking them out of action. It can eventually recycle them back to the surface, where they can respond to neurotransmitters again.

The researchers looked at receptors that respond to a neurotransmitter called glutamate, which is implicated in memory and learning. In mice that were genetically altered to make human APOE4, the researchers found that APOE4 prevented the cells from accomplishing a vital step in learning - becoming more sensitive to repeated signals.

The researchers also studied the mice's hippocampus - an area of the brain vital to learning - to see how it would respond to extracts from the brain of a human with Alzheimer's. The extract prevented both normal and genetically altered mice from processing incoming signals; however, the normal mice could recover from this suppression, while the mice with APOE4 could not.

Dr. Herz and his colleagues hypothesized that APOE4 exerted its effects by interacting with the receptors for a molecule called Reelin, which keeps brain cells more sensitive to each other. Both APOE4 and Reelin bind to the same receptor. When Reelin binds to it, the combination triggers a biochemical cascade that makes the glutamate receptor more sensitive to incoming signals.

The researchers showed that APOE4 prevents the Reelin-binding

receptor from being recycled back to the surface. With fewer receptors, the nerve cell can't bind much Reelin, no matter how much is around. Without Reelin's effects, the cell doesn't respond as vigorously to glutamate, and doesn't "learn" as well.

Knowing how a biological system works doesn't automatically translate to clinical use, Dr. Herz cautioned. "Although these findings constitute a milestone in our understanding of how APOE4 becomes such a potent risk factor for Alzheimer's disease, potential drugs that might come from this finding would still require years of development," he said.

"The question is, now that we've apparently identified what's going on, can we do anything about this disease process at the fundamental molecular level? That's what we're working on right now," Dr. Herz said.

Provided by UT Southwestern Medical Center