Study pinpoints key mechanism in brain development, raising questions about use of antiseizure drug

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Researchers at the Stanford University School of Medicine have identified a key molecular player in guiding the formation of synapses — the all-important connections between nerve cells — in the brain. This discovery, based on experiments in cell culture and in mice, could advance scientists' understanding of how young children's brains develop as well as point to new approaches toward countering brain disorders in adults.

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The new work also pinpoints, for the first time, the biochemical mechanism by which the widely prescribed drug gabapentin (also marketed under the trade name Neurontin) works. "We have solved the longstanding mystery of how this blockbuster drug acts," said Ben Barres, MD, PhD, professor and chair of neurobiology. The study shows that gabapentin halts the formation of new synapses, possibly explaining its therapeutic value in mitigating epileptic seizures and chronic pain. This insight, however, may lead physicians to reconsider the circumstances in which the drug should be prescribed to pregnant women.

The paper, published online Oct. 8 in the journal *Cell*, looks at the interaction between neurons — the extensively researched nerve cells that account for 10 percent of the cells in the brain — and the less-studied but much more common brain cells called astrocytes. Much work has been done on how neurons transmit electrical signals to each other through synapses — the nanoscale electrochemical contact points between neurons. It is the brain's circuitry of some 100 trillion of these synapses that allow us to think, feel, remember and move.

It is commonly agreed that the precise placement and strength of each person's trillions of synaptic connections closely maps with that person's cognitive, emotional and behavioral makeup. But exactly why a particular synapse is formed in a certain place at a certain time has largely remained a mystery. In 2005, Barres took a big step toward explaining this process when he and his colleagues discovered that a protein astrocytes secrete, called thrombospondin, is essential to the formation of this complex brain circuitry.

Still, no one knew the precise mechanism by which thrombospondin induced synapse formation.

In this new study, Barres, lead author Cagla Eroglu, PhD, and their colleagues demonstrate how thrombospondin binds to a receptor found on neurons' outer membranes. The role of this receptor, known as alpha2delta-1, had been obscure until now. But in an experiment with mice, the scientists found that neurons lacking alpha2delta-1 were unable to form synapses in response to

thrombospondin stimulation.

And when the researchers grew neurons in a dish that were bioengineered to overexpress this receptor, those neurons produced twice as many synapses in response to stimulation with thrombospondin than did their ummodified counterparts.

The new discovery about alpha2delta-1's key role in synapse formation carries important implications for understanding the cause of pain and of epilepsy and developing improved medications for these conditions.

It was already known that alpha2delta-1 is the neuronal receptor for gabapentin, one of the world's most widely administered medications. Gabapentin is often prescribed for epilepsy and chronic pain, and its off-label use for other indications is widespread. Up to now, the molecular mechanism of gabapentin's action — what, exactly, it's doing to counter seizures or chronic pain — was unknown. But both syndromes may involve excessive numbers of synaptic connections in local areas of the brain.

In their new study, Barres and his colleagues found that when gabapentin was administered in developing mice, it bound to alpha2delta-1, preventing thrombospondin from binding to the receptor and, in turn, impeding synapse formation. Likewise, by blocking thrombosponin, gabapentin may reduce excess synapse formation in vulnerable areas of the human brain.

Barres noted that he and his colleagues found that gabapentin does not dissolve pre-existing synapses, but only prevents formation of new ones. That greatly diminishes gabapentin's potential danger to adults. In mature human brains, astrocytes ordinarily produce very little thrombospondin, and adult neurons don't form many new synapses, although some new synapses do continue to be formed throughout life — for example, in a part of the brain where new memories are laid down and at sites of injury to neurons, such as occurs after a stroke.

But the new findings raise questions about gabapentin's effect in situations where synapse formation is widespread and crucial, most notably in pregnancies. The vast bulk of the brain's synapses are formed during gestation and the very early months and years after birth. Because gabapentin easily crosses the placental barrier, it could potentially interfere with a fetus' rapidly developing brain just when global synapse formation is proceeding at breakneck speed.

"It's a bit scary that a drug that can so powerfully block synapse formation is being used in pregnant women," Barres said. "This potential effect on fetal brains needs to be taken seriously. Right now, doctors have the view that gabapentin is the safest anticonvulsant. There is no question that pregnant women with epilepsy who have been advised by their neurologists to continue their anticonvulsant treatment with gabapentin during their pregnancy should definitely remain on this drug until instructed otherwise. But there is no long-term registry being kept to track gabapentin-exposed babies. Our findings are saying that we need to be following up on these newborns so that their cognitive performance can be studied as they grow older."

Eroglu, then a postdoctoral researcher in Barres' laboratory, is now an assistant professor of cell biology at Duke University in Durham, N.C. Other Stanford co-authors were Nicola Allen, PhD; Michael Susman; Nancy O'Rourke, PhD; Chan Young Park, PhD; Engin Ozkan, PhD; Chandrani Chakraborty; Sara Mulinyawe; Andrew Huberman; PhD; Eric Green, MD, PhD; Ricardo Dolmetsch, PhD; Christopher Garcia, PhD; and Stephen Smith, PhD. Funding was provided by the National Institute of Drug Addiction; the National Heart, Lung and Blood Institute; the National Institutes of Health; the Human Frontiers Scientific Program and a Helen Hay Whitney postdoctoral fellowship.

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