MedicalXpress

Study May Explain How A Well-Known Epilepsy and Pain Drug Works

October 12 2009

(PhysOrg.com) -- A Duke University Medical Center researcher who spent years looking for the signals that prompt the brain to form new connections between neurons has found one that may explain precisely how a well-known drug for epilepsy and pain actually works.

The finding may also point to new therapies for brain injury and neuropathic pain.

The role of neurons in the brain and nervous system is well known, but astrocytes, a different type of brain cell, still are largely a mystery.

Duke scientist Cagla Eroglu, PhD, has discovered a receptor that receives messages from astrocytes so that the brain can form excitatory synapses, the cell-to-cell connections that can become overactive in conditions such as epilepsy.

Working with a team of scientists from other institutions, Eroglu found this receptor is also blocked by the anti-convulsant drug gabapentin (Neurontin™).

The study appears online in the latest issue of *Cell*.

“The study links astrocytes and their role in synapse formation to diseases, so if the normal process goes wrong, this may explain why people get epilepsy, why epilepsy gets worse, or why they have neuropathic pain,” said Eroglu, assistant professor in the Duke

Department of Cell Biology.

“It’s a fine balance, because synapse formation has to occur during development for neurons to transmit brain signals, but if this happens in an uncontrolled manner in the adult brain, it could lead to these debilitating conditions.”

Eroglu spent years looking for this neuronal receptor, which prompts synapse formation.

“The key clue came when we chopped thrombospondin, a protein that comes from astrocytes and triggers establishment of synapses, into small fragments and put it onto neurons. We found that a specific portion of thrombospondin, the EGF-like domain, was equally effective as the whole protein. This gave me the clue that was necessary to identify its neuronal receptor. However it took me a while to do so."

On advice she heard from a lecture by another scientist, Nobel laureate Linda Buck -- “Spend more time thinking about your experiments and your results before designing new experiments” -- Eroglu took a short break from her bench-work, went home, and reasoned her way through several possibilities, finally settling on the idea that a receptor for the molecule gabapentin might be a key to regulating the formation of synapses.

Excited, she returned to the lab and verified the interaction between proteins. “When I discovered that gabapentin completely blocked synapse formation between isolated neurons, I could not sleep for days until I replicated the results.”

The research also points to the need for further research on gabapentin’s actions, Eroglu said. The drug gabapentin strongly blocks the receptor, reducing synapse formation in rodents.

“The question is whether gabapentin might be linked with or interfere with cognitive ability, especially in the developing fetus of a woman taking the drug to control epilepsy," Ergolu said. "But of course this needs to be balanced with the mother’s need to prevent her from having seizures.”

“Likewise, while it is rare that a young child is given gabapentin for seizures, I think scientists need to study whether this possibly could be linked with side effects of this drug in children such as hyperactivity, irritability and maybe even cognitive problems," she said.

Gabapentin may also be a boon for certain conditions that haven’t yet been studied, she said. For example, in soldiers who have severe head wounds, many go on to develop epilepsy in the months after their injuries.

“Maybe their injuries trigger the development of excess excitatory synaptic connections, and blocking or modulating this preemptively with gabapentin could help to prevent in this situation.”

She said that understanding how the receptor works could also help patients who have neuropathic pain because of advanced diabetes or an injury.

“Neuropathic pain is not perceived by patients in the same way as other types of pain,” Eroglu said.

“Regular anti-analgesic drugs do not successfully ease this type of pain. Based on our findings it is possible that aberrant new synaptic connections that occur after injury contribute to neuropathic pain, and gabapentin might work by breaking this cycle of synapse formation.”

Provided by Duke University (news : web)