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Dodging the cognitive hit of early-life seizures

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About half of newborns who have seizures go on to have long-term intellectual and memory deficits and cognitive disorders such as autism, but why this occurs has been unknown. In the December 14 *Journal of Neuroscience*, researchers at Children's Hospital Boston detail how early-life seizures disrupt normal brain development, and show in a rat model that it might be possible to reverse this pathology by giving certain drugs soon after the seizure.

A research team led by Frances Jensen, MD, in the Department of Neurology and Division of Neuroscience at Children's, studied seizures in a rat model to see how they affected brain development at the cellular and molecular level, and whether these effects could be countered. They were particularly interested in the effect of seizures on synapses, the connections between neurons through which the brain is wired, since infancy is a time of rapid synapse development.

Examination of tissue from the hippocampus, a part of the brain important in learning and memory, showed that after seizures, the newborn rats had a far smaller pool of inactive or "silent" synapses, which normally predominate soon after birth. Instead, more synapses than normal had been converted to an excitable form by acquiring more so-called AMPA receptors. (AMPA stands for alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid.)

While an excitatory brain state and strengthening of synaptic connections are normal and necessary for cognitive development, Jensen's team

found that seizures exaggerated excitation and synaptic strengthening too soon, to the point where synapses lost their flexibility to change in response to input from the environment, a quality known as plasticity. All these changes were evident within 2-3 days after the seizure.

"Our results show that once a seizure occurs, brain tissue has less synaptic plasticity," says Jensen. "Seizures have 'fixed' the synapses so they have much less potential to respond to experience." Since early-life seizures can lead to epilepsy, Jensen believes the results may help explain the cognitive impairments seen in many people with epilepsy.

After a seizure, the rats' brain tissue also showed a decrease in long-term potentiation (LTP), a change in the strength of synaptic connections that is critical in learning and memory, indicated by reduced electrical responses to stimulation of neurons. LTP is a widely accepted molecular measure of learning.

These effects appear to be reversible, however. When the rats were given a drug that blocks AMPA receptors, known as NBQX, immediately to 48 hours after seizures, these problems were reversed: Inactive synapses and LTP were preserved, and the protective effects lasted into adulthood.

Since drugs similar to NBQX are already FDA-approved for other indications, Jensen believes these results might eventually lead to a clinical trial in newborns who have had seizures.

"Because we can reverse the strengthening of synapses, we might be able to modify the disease after the fact, which is one step in the right direction toward thinking about potential strategies for cures," she says. "Epilepsy has many mechanisms and potential therapeutic targets, but this is one that may be important in undoing the cognitive effects that epilepsy may have."

Some 80-120 newborns per 100,000 births each year in the U.S. suffer seizures, often caused by brain damage from a shortage of oxygen around the time of birth.

Provided by Children's Hospital Boston