Study raises questions about use of anti-epilepsy drugs in newborns

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A brain study in infant rats demonstrates that the anti-epilepsy drug phenobarbital stunts neuronal growth, which could prompt new questions about using the first-line drug to treat epilepsy in human newborns.

In *Annals of Neurology* EarlyView posted online May 11, researchers at Georgetown University Medical Center (GUMC) report that the anti-epilepsy drug phenobarbital given to rat pups about a week old changed the way the animals' brains were wired, causing cognitive abnormalities later in life.

The researchers say it has been known that some of the drugs used to treat epilepsy increase the amount of neurons that die shortly after birth in the rat brain, but, until this study, no one had shown whether this action had any adverse impact on subsequent brain development.

"Our study is the first to show that the exposure to these drugs -- and just a single exposure -- can prevent brain circuits from developing their normal connectivity, meaning they may not be wired correctly, which can have long-lasting effects on brain function," says the study's senior investigator, Karen Gale, Ph.D., a professor of pharmacology at GUMC. "These findings suggest that in the growing brain, these drugs are not as benign as one would like to believe."

For their study, the Georgetown researchers studied four agents including phenobarbital.

"The good news is not all anti-epilepsy drugs have this disruptive effect in the animal studies," Gale says.

The researchers found that the anti-epilepsy drug levetiracetam did not stunt synaptic growth. Animals treated with a third drug, lamotrigine, showed neural maturation, but it was delayed. An additional finding involved melatonin. When added to phenobarbital, it appeared to prevent the persistent adverse neural effects in the rat pups. Melatonin has been used clinically to protect cells from injury in humans.

"Many clinicians have been advocating for a reexamination of the use of these drugs in infants, and our findings provide experimental data to support that need," says the study's co-lead investigator, Patrick A. Forcelli, Ph.D., a postdoctoral fellow in the department of pharmacology and physiology at GUMC. "Phenobarbital has been used to treat seizures for over 100 years -- well before a Food and Drug Administration approval process was established-- and for more than 50 years, it has been the first drug of choice in the treatment of seizures in neonates."

According to the Epilepsy Foundation, epilepsy affects more than 300,000 Americans under the age of 15. Seizures in neonates are relatively common, and seizure incidence peaks in the first year of life and remains at a high level up to age four.

Recent studies of IQ and other measurements of cognitive function in children have suggested that exposure to certain anti-epilepsy drugs, either in utero or infancy, affects brain function, but the issue is highly controversial, Forcelli says.

"Seizures do not happen to a normal healthy brain," he says. "They are typically associated with, or are a result of, an injury or another neurological condition. So the issue is: what causes later deficits in function -- the underlying condition, the seizures, or the drug used to

treat the seizures or some combination of these? Our study in otherwise normal animals suggests that drugs by themselves can be a significant factor."

The Georgetown researchers say their study was designed to look directly at the effect of the different drugs on normal growth of brain neural networks in otherwise normal animals.

This kind of study can only with research in animals, in which each component (condition, seizure and drug) can be controlled and examined separately and in combination.

This kind of study can only be performed in animal models, in which the drug effects can be examined separately from the effects of either seizures or other complications.

"We were looking for the link between acute drug actions seen in a week-old rat pup and the long-term behavioral deficits we and others have seen in rats and humans," Forcelli says.

The researchers measured communication between neurons in an area of the brain known to be sensitive to anti-epilepsy drugs in baby rats that were 10, 14, or 18 days old. In normal, untreated rats, there was a dramatic increase in communication between neurons in this area during this eight-day period. But this maturation of neurons in the critical brain circuit was not seen in rats that had been treated a week earlier with a single therapeutic dose of phenobarbital or a different drug, phenytoin.

The researchers also tested the effect of the drugs after the pups reached early childhood, and found that those treated with phenobarbital were slow to learn.

"This is an important bridge between molecules and behavior that helps

us to understand how early life drug exposure can permanently alter behavioral function in later life of the rats," Forcelli says.

The research group is now planning to find out how the drugs affect brain development in infant animals that also have seizures.

Provided by Georgetown University Medical Center