Preventing autism after epilepsy

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(Medical Xpress) -- Early-life seizures are known to be associated with autism, and studies indicate that about 40 percent of patients with autism also have epilepsy. A study from Boston Children's Hospital finds a reason for the link, and suggests that an existing drug, already shown to be safe in children, could help prevent autism from developing in newborns who have seizures. Findings were published May 2 in the online journal PLoS ONE.

Led by Frances Jensen, MD, in the Department of Neurology and the F.M. Kirby Neurobiology Center at Boston Children's Hospital, the study suggests that seizures over-activate a biochemical pathway previously linked to autism, known as the mTOR pathway, and that this alters the fast-forming circuitry in infants' developing brains.

In a rat model, Jensen and colleagues showed that early seizures not only resulted in epilepsy later in life, but also produced autistic-like behavior. They further showed that disabling the mTOR pathway - by giving the drug rapamycin before and after seizures - prevented development of abnormal patterns of connections (synapses) between brain cells, reduced later-life seizures and eased autistic-like symptoms.

"In children, there is overlap between epilepsy and autism, and epilepsy early in life has been linked to later autism," says Jensen of Boston Children's Hospital. "Our findings show one of probably many pathways that are involved in this overlap - importantly, one that is already a therapeutic target and where treatment can reverse the later outcome."

Specifically, the study demonstrated that a group of signaling molecules known collectively as the mTOR pathway shows increased activation after a seizure. This increased signaling - above and beyond the surge that normally occurs early in life - disrupted the normal balance of synapse and circuit development to produce epilepsy and altered social behavior. Rapamycin treatment inhibited mTOR signaling, reducing susceptibility to seizures and preventing seizure-induced changes in the synapses.

The study uncovers a new link whereby epilepsy and autism may interact in early development. Last December, Jensen and colleagues published a related study finding that seizures exaggerated excitation and synaptic strengthening too soon in a rat model, causing synapses to lose their plasticity -- their ability to reconfigure in response to input from the outside world. When they gave the rats a drug called NBQX, which blocks receptors associated with excitation, these problems were reversed.

The mTOR pathway is already known to be over-active in tuberous sclerosis complex (TSC) a genetic disorder treated at Boston Children's that often includes epilepsy and autism. The hospital is currently conducting a clinical trial of rapamycin in children with TSC.

"Our study suggests that even without tuberous sclerosis, seizures are inducing the mTOR pathway, and might on their own be contributing to the development of autism," says Jensen. "It appears that blocking the mTOR pathway briefly after the initial seizures may reduce the risk of later epilepsy and autism. This research also suggests that the fields of epilepsy and autism may inform each other about new treatment targets."

For further background, see this feature published last year in *Nature Medicine*.

Provided by Children's Hospital Boston