

Stimulating Environment Reverses Effects of Seizures in Young Children

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Children with epilepsy often struggle with cognitive and psychological effects of seizures, such as memory deficits and depression. Using experimental animal models and gene expression analyses, Sookyong Koh, MD, PhD, at Children's Memorial, has been able to demonstrate the ways in which social isolation contributes to the cognitive and psychological consequences of epilepsy, and how an enriched environment actually reverses the damaging effects of seizures in young children.

"Social isolation is a very big problem for children with epilepsy," says Koh. "Basic science in my laboratory supports the concept that an enriched environment is therapeutic. Armed with insights from this research, pediatricians can respond when parents ask 'what can I do?'"

Working with rats whose ages corresponded to children 2 to 5 years of age, Koh's experimental paradigm attempted to recreate the experience of growing up in social isolation vs. an environment with sensorimotor stimuli and social interaction, with and without seizures. After 7 to 10 days, each group was tested for explorative behavior in an unfamiliar open space, which for rats is anxiety-provoking.

Just being reared in isolation, without seizures, caused marked anxiety, compared to the environment enrichment group that explored freely. Seizures in addition to isolation produced a huge detrimental effect, whereas rats with seizures reared in an enriched environment fared significantly better.

Koh's team then used the microarray gene expression profiling technology to screen both groups for common genes that were affected by seizures and were then upregulated or downregulated depending on the environment. "We screened around 123 000 genes and had no preconceived notions about the genes we were going to find," says Koh.

For the first time, through this research 12 genes that are impacted by seizures and affected by environmental enrichment were identified. Seven of the top genes are transcription factors, which regulate expression of other genes.



Sookyong Koh, MD, PhD, with her patient Cara Flaherty, who has Dravet syndrome with truncation of a sodium channel gene. Cara has benefited greatly from intensive educational intervention, in addition to early diagnosis and treatment.

Some of the identified genes, such as *Arc*, *Homer1a*, and *Egr1*, were known to be implicated in learning and memory, but never before in a disease setting. It was not known previously that these genes are involved in epilepsy.

Koh's team also experimentally demonstrated that these genes are functionally important. "We were able to show in a rat model that overexpression of the *Arc* gene can reverse behavioral deficits related to seizures and social isolation," explains Koh. "We gave the *Arc* gene to the animal after a seizure and social isolation and saw an increase in explorative behavior. This showed that the behavior we saw really was a result of gene expression."

Strikingly, Koh's gene expression analyses showed that the negative effects of a prolonged seizure – effects on the expression of genes connected with memory and of inflammation-related genes associated with seizure susceptibility – were completely reversed by exposure to an environment rich in stimuli and opportunities for social interaction.

Koh's team also identified a gene tied to seizures and depressive behavior (serotonin receptor 5B). In a similar experiment, her team demonstrated that the detrimental downregulation of this gene as a consequence of seizures was reversed by environmental enrichment.

Stressing that the conclusions of her research directly translate to clinical care, Koh says: "Even after a prolonged seizure, the young brain has an innate ability to heal and recover. We can minimize the detrimental effect of prolonged seizures by helping that healing process through environmental enrichment. Social isolation hampers that innate ability of young children to recover from the impact of seizures. It is important for physicians and families to know and apply this new understanding, make sure that children with epilepsy are not socially isolated, that they engage in stimulating activities and are encouraged to pursue interests."