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Barbara McMakin
nindspressteam@ninds.nih.gov
(301) 496-5751

Silky smooth brain implants may help stop spread of epilepsy

NIH-funded study suggests role for adenosine in molecular processes involved in epilepsy

Silk has cat-walked straight off the runway and into the lab. According to a new study, silk implants placed in the brain and designed to release a specific chemical, adenosine, may help stop the progression of epilepsy.

The epilepsies are a group of neurological disorders associated with recurring seizures that tend to become more frequent and severe over time. Adenosine decreases neuronal excitability and helps stop seizures. Earlier studies have suggested low levels of adenosine may be linked to epilepsy.

Rebecca L. Williams- Karnesky, Ph.D. and her colleagues from Legacy Research Institute, Oregon Health and Sciences University (OHSU), and Tufts University wanted to see if a therapy they created would stop the spread of epilepsy. They had developed silk implants for the brain that released a specific amount of adenosine over 10 days. In an earlier study, it was found that the implants were effective in stopping seizures in rats while adenosine was being released. However, in the current study, although adenosine was released from the silk implants for only 10 days, there was reduction in seizure activity in rats for at least 3 months.

In this study, the rats did not receive the implants until they had experienced a number of seizures. The researchers noted that many studies investigating anti-epileptic drugs often test the treatments too early. "If the therapy interferes with the trigger for epilepsy development then the trigger is weakened and subsequent epilepsy is less severe. However, this is not necessarily indicative of a stop in the progression of the disease," said Detlev Boison, Ph.D., senior author of the paper from Legacy Research Institute and OHSU.

"To avoid interference with the epilepsy-triggering mechanisms, we waited until all animals developed an early stage of epilepsy. In this model, the disease is life-long: seizures become more frequent and worsen with time. Therefore, we challenged ourselves to attempt treatment at a stage where epilepsy had already been established," Dr. Boison continued.



One mechanism involved in epilepsy is an increase in mossy fiber sprouting — the formation of new excitatory circuits in the part of the brain where seizures are thought to originate. At the end of the experiment, animals that had been treated with the adenosine-releasing silk implant showed less sprouting than animals that were not given the drug. "Based on our findings that 10 days of adenosine delivery prevented the sprouting of mossy fibers long-term, for 3 months, we predict a permanent beneficial effect of our adenosine therapy. However, this assumption needs to be validated in long-term experiments that go beyond 3 months," said Dr. Boison.

It has been suggested that seizures can cause epigenetic changes that may worsen epilepsy. Epigenetic modifications are chemical reactions that change the way genes are turned on or off without altering the DNA code (the letters that make up our genetic background). Specifically, these changes happen when a molecule known as a methyl group blocks a portion of DNA, affecting which genes are accessible and can be turned on. DNA methylation status — that is, if methyl groups have been added (methylated) or taken away (demethylated) — may play an important role in epilepsy.

"We know that there are mutations that are associated with epilepsy. However, there are few people such as Dr. Boison who are doing this type of work, focusing not just on genetic mutations but how the genes are regulated," said Vicky Whittemore, Ph.D. program director at the National Institute of Neurological Disorders and Stroke.

The results reported in the paper provided evidence that tweaking adenosine levels affected DNA methylation in the brain. Specifically, greater amounts of adenosine were associated with lower levels of DNA methylation. For example, epileptic rat brains that had received the adenosine-releasing silk implants exhibited DNA methylation levels close to brains of normal rats.

These findings suggest that the silk implants may be a potential therapy for epilepsy. "Adenosine-releasing silk is a biodegradable implant. Once the release of adenosine is finished, the silk will completely dissolve. This is an ideal set-up for a transient preventative treatment," said Dr. Boison. "Clinical applications could be the prevention of epilepsy following head trauma or the prevention of seizures that often — in about 50% of patients — follow conventional epilepsy surgery. In this case, adenosine-releasing silk might be placed into the resection cavity in order to prevent future seizures."

However, before the silk implants are ready for their close-up future studies will need to determine their optimal use. According to Dr. Boison, "We need to look into the efficacy of different doses of adenosine, the duration of adenosine release, and various time points of intervention."

"This work is important because there are still 25-30% of people with epilepsy who do not have effective therapies. This research may help us to prevent epilepsy in people at risk for the disorder, such as individuals who have experienced head trauma," said Dr. Whittemore.

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References:



Rebecca L. Williams-Karnesky et al. "Epigenetic changes induced by adenosine augmentation therapy prevent epileptogenesis." *Journal of Clinical Investigation*, July 25, 2013.

For more information about epilepsy, please visit: http://www.ninds.nih.gov/disorders/epilepsy/epilepsy.htm

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