Researchers identify possible trigger point of epileptic seizures

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Researchers at the Stanford University School of Medicine have identified a brain-circuit defect that triggers absence seizures, the most common form of childhood epilepsy.

In a study to be published online Aug. 21 in Nature Neuroscience, the investigators showed for the first time how defective signaling between two key brain areas — the cerebral cortex and the thalamus — can produce, in experimental mice, both the intermittent, brief loss of consciousness and the roughly three-times-per-second brain oscillations that characterize absence seizures in children. Young patients may spontaneously experience these seizures up to hundreds of times per day, under quite ordinary circumstances.

The new findings may lead to a better understanding of how ordinary, waking, sensory experiences can ignite seizures, said John Huguenard, PhD, the study's senior author.

Epilepsy, a pattern of recurrent seizures, will affect about one in 26 people over their lifetime. Absence, or petit-mal, seizures — the form that epilepsy usually takes among children ages 6-15 — feature a sudden loss of consciousness lasting 15 seconds or less. These seizures can be so subtle that they aren't noticed, or are mistaken for lack of attention. The patient remains still for several seconds, as if frozen in place. Usually, a person who experiences an absence seizure has no memory of the episode.

"It's like pushing a pause button," said Huguenard, professor of neurology and neurological sciences and of molecular and cellular physiology.

Inside the brain, however, things more resemble an electrical storm than a freeze-frame.

The brain is, in essence, a complicated electrochemical calculating machine employing circuits that process information and share it with other, often-remote circuits, resulting in networks of sometimes staggering complexity. A nerve cell can be thought of as a long, branching wire that can transmit electrical signals along its length and then relay these signals to up to thousands of other nerve cells by secreting specialized chemicals at points of contact with other "wires." Depending on the nature of the signaling interaction, the result can be either excitatory (increasing the likelihood that the next nerve cell in the relay will fire its own electrical impulse) or inhibitory (decreasing that likelihood).

During an absence seizure, the brain's electrical signals spontaneously coalesce into rhythmic oscillations, beginning in the neighborhood of two important brain areas, the cortex and the thalamus. Exactly where or how this pattern is initiated has been a source of controversy, said the study's lead author, Jeanne Paz, PhD, a postdoctoral researcher in Huguenard's lab.

"In order to develop better therapies, it is important to understand where and how the oscillations originate," Paz said.

The cortex and thalamus share an intimate relationship. The cortex, like a busy executive, assesses sensory information, draws conclusions, makes decisions and directs action.

To keep from being constantly bombarded by distracting sensory information from other parts of the body and from the outside world, the cortex flags its activity level by sending a steady stream of signals down to the thalamus, where nearly all sensory signals related to the outside world are processed for the last time before heading up to the cortex. In turn, the thalamus acts like an executive assistant, sifting through sensory inputs from the eyes, ears and skin, and translating their insistent patter into messages relayed up to the cortex. The thalamus carefully manages those messages in response to signals from the cortex.

These upward- and downward-bound signals are conveyed through two separate nerve tracts that each stimulate activity in the other tract. In a vacuum, this would soon lead to out-of-control mutual excitement, similar to a microphone being placed too close to a P.A. speaker. But there is a third component to the circuit: an inhibitory nerve tract that brain scientists refer to as the nRT. This tract monitors signals from both of the other two, and responds by damping activity. The overall result is a stable, self-modulating system that reliably delivers precise packets of relevant sensory information but neither veers into a chaotic state nor completely shuts itself down.

In bioengineered mice that the Stanford team studied with Wayne Frankel, PhD, of the Jackson Laboratory in Bar Harbor, Maine, this circuit is broken because the GluA4 receptor, a protein component of cells critical to the stimulation of nRT cells, is missing. Notably, these mice are prone to intermittent absence seizures. The researchers aimed to find out why, by separately studying the mouse's key corticothalamic-circuit components. Using a technique called optogenetics, they were able to selectively switch each of the two stimulatory tracts' signal transmissions on or off at will.

The researchers observed that, as expected, signals from one of the two tracts failed to excite the receptor-deficient mice's inhibitory nRT cells.

Oddly, though, signals from the other tract continued to get through to the nRT tract just fine — "a paradoxical and totally surprising result," said Huguenard.

This leaves nRT receiving signals from one tract, but not the other, which upsets the equilibrium usually maintained by the circuit. As a result, one of its components — the thalamocortical tract — is thrown into overdrive. Its constituent nerve cells begin firing en masse, rather than faithfully obeying the carefully orchestrated signals from the cortex. This in turn activates the nRT to an extraordinary degree, because its contact with the thalamocortical tract is not affected in these mice.

Huguenard estimates that, typically, only a very small percentage of nRT cells are firing at a given time. In the face of over-amped signaling from the thalamocortical tract, however, the fraction of excited nRT nerve cells rose much higher, perhaps as much as 50 percent — enough to effectively silence all signaling from the thalamus to the cortex — a key first step in a seizure.

But the shutdown was transitory. A property of thalamic cells (like other nerve cells) is that when they've been inhibited they tend to overreact and respond even more strongly than if they had been left alone. After a burst of nRT firing, this tract's overall inhibition of the thalamocortical tract all but halted activity there for about one-third of a second. Like boisterous schoolchildren who can shut up only until the librarian leaves the room, the thalamocortical cells resumed shouting in unison as soon as the inhibition stopped, and a strong volley of signaling activity headed for the cortex. Then the nRT's inhibitory signaling recommenced, and the stream of signals from the thalamus to the cortex ceased once again.

This three-Hertz cycle of oscillations consisting of alternating quiet and exuberant periods repeated over the course of 10 or 15 seconds was the

electrophysiology of a seizure.

Whether the specific nRT defect in the bioengineered mice is important in human absence seizures is not yet known, Huguenard cautioned. Most individuals who suffer from these seizures appear to have "normal" nerve cells (individually indistinguishable from those of non-epileptics) and normally formed circuits as well. But now his group has a model experimental system with which they can try to determine why ordinary experiences can trigger these seizures in everyday life. Behavioral experiments are under way in his lab to see what kinds of common sensory exposures can trip off a similar circuit malfunction in normal mice. The resulting observations may someday help patients control their own exposures to minimize seizures, Huguenard said.

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