Rats' stroke-induced seizures stopped with pulse of light

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(Medical Xpress)—Stanford University School of Medicine scientists have shown that a structure deep within the brain is a crucial component of recurring seizures that can arise as a delayed consequence of a cerebral stroke. This structure, called the thalamus, is known as a relay station routing inputs from the senses to the brain's higher cognitive processing centers in the cerebral cortex. But the thalamus has never before been implicated in post-stroke seizures.

In a study published online Nov. 7 in *Nature Neuroscience*, the investigators proved that the thalamocortical tract—a nerve bundle that among other things conveys sensory information from the thalamus to many parts of the more-expansive cerebral cortex, the outermost layer of the mammalian brain—is intimately involved in post-cerebral-stroke seizures.

The researchers first induced strokes to a small spot in rats' somatosensory cortex, the part of the cortex that processes information such as touch and pain. This rendered the rats vulnerable to seizures starting within weeks. Employing a combination of sophisticated techniques, the scientists engineered a method of remotely detecting electrical activity in the thalamocortical tract that accompanied the rats' seizures and, at the press of a button, shutting down the activity in the tract. Doing this invariably stopped a rat's seizure.

"If we prevent the thalamus from participating in the seizure, we actually block the seizure—instantly," said John Huguenard, PhD, professor of

neurology and neurological sciences and of molecular and cellular physiology. Huguenard is the senior author of the study. In 2011, he and his colleagues published a study, also in Nature Neuroscience, implicating the thalamus in absence, or petit mal, epilepsy, the most common form of epilepsy among children. Strokes, on the other hand, are much more likely to afflict older people.

"The current thinking in the field," Huguenard said, "has been that the thalamus isn't an integral part of the brain circuitry that goes haywire during the recovery phase after a cortical stroke." After all, he noted, in humans the thalamus and the cerebral cortex are several inches apart—in the central nervous system, that's considered a long distance.

But the thalamus and the cortex are intimate partners in an ongoing two-way communication in which the thalamus receives signals from the outside world, tunes and bundles these signals into packets that it perpetually punts to relevant parts of the cortex, and then receives feedback from the cortex—such as, "I'm busy now, so I'm ignoring you," or "Whoa, what did you just say?" Constant communication requires sturdy transmission lines, and the thalamus and cortex are connected by nerve bundles that transmit in opposite directions. The thalamocortical tract is the output line from the thalamus to the cortex.

The researchers' first exploration in the stroke-affected rats, according to Jeanne Paz, PhD, a research associate in Huguenard's laboratory and the lead author of the new study, took place in the part of the thalamus that corresponds to the cortical area where the stroke had occurred. "Not surprisingly, we saw cell death there," Paz said. Huguenard, Paz and their teammates had correctly assumed the rats' strokes, although they were occurring far from the thalamus, would damage not only brain cells resident in the somatosensory cortex but also the tips of nerve fibers ascending from the thalamic area that bundles touch-related inputs and routes them to the somatosensory cortex. Injury to its tip is often enough

to cause an entire nerve cell to die.

"What was surprising," said Paz, "was that those thalamocortical cells that had been injured by the stroke but had survived became hyperexcitable." Tests showed that these nerve cells were capable—all too capable, in fact—of generating abnormal electrical activity.

The researchers then turned to optogenetics, a technology pioneered at Stanford by study co-author Karl Deisseroth, MD, PhD, professor of bioengineering and of psychiatry and behavioral science. They inserted into thalamocortical-tract nerve fibers (and only those fibers) the gene for a photosensitive protein that sits on a fiber's surface and reacts to yellow laser light by inhibiting electrical impulses that might otherwise propagate along the fiber. They also implanted remote-recording devices into each rat's thalamus so the rats could be monitored while fully alert and ambulatory, and they observed that seizures were invariably accompanied by precisely the same abnormal electrical activity emanating from the thalamus. Laser light could be transmitted straight to the area of interest in the thalamus via connecting optical fibers.

The Stanford researchers also automated the apparatus so that a computer, sensing the onset of thalamocortical-tract electrical activity that closely accompanies the onset of a seizure, could immediately direct a yellow-light laser pulse to the thalamus. This would invariably interrupt the seizure.

This demonstrated, in defiance of conventional wisdom, that thalamic involvement was essential to post-cortical-stroke seizure activity. "This has never been shown before," Paz said.

"The study results should not be interpreted to mean that we've shown that seizures arising from a cortical stroke originate in the thalamus," Huguenard said. "We haven't shown that. They may well arise in the

injured, but surviving, cortical nerve cells surrounding the zone where the stroke itself occurred. But regardless of the seizures' point of origin, what's important is that we can block those seizures by shutting off a compact group of cells in the thalamus." So in principle, regardless of where a stroke had occurred in the cortex (which occupies a relatively vast stretch of territory), a device capable of blocking seizures resulting from a cortical stroke could be implanted in the thalamus, which occupies a much smaller terrain.

In theory, such a device might be superior to drug therapy, because it would not only respond instantly to seizures (while letting the thalamus to operate unimpeded during the intervening periods between seizures) but would target only a single group of cells immediately involved in the seizure circuitry, minimizing side effects. In addition, this new approach would not directly affect cerebral cortical function at all, thus further reducing side effects.

Huguenard cautioned, however that any therapeutic applications in humans are still a good decade off. "This is not something that's going to happen today or tomorrow," he said. "It would require inserting genes into people's living brain cells. And we're still a ways from being able ensure the safety of gene therapy. This would also require being able to produce a reliable, battery-operated device that could be permanently implanted in the brain."

However, Huguenard added, "even a conventional drug that very specifically targeted this small group of cells we've implicated would be a great step forward in epilepsy treatment."

More information:
med.stanford.edu/ism/2011/august/huguenard.html

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