



Faulty Connection

Disturbed transmission of signals in the cerebrum promises new findings for epilepsy research

A research group at the Cluster of Excellence BrainLinks–BrainTools led by neurobiologist Prof. Dr. **Carola Haas**, also a member of Bernstein Center Freiburg, has discovered a mechanism that could be involved in the development of temporal lobe epilepsy. The team, which conducts most of its work at the Department of Neurosurgery of the Freiburg University Medical Center, explained in an article for the journal *Cerebral Cortex* how the modification of particular synapses and nerve cells boosts the transmission of signals from the temporal lobe, thus increasing the potential for seizures.

Using precise tracing techniques and genetically modified mice, the researchers visualized fiber bundles and synaptic contacts between the temporal lobe and the hippocampus. In the healthy brain, a signaling path involved in language understanding and visual recognition leads from the edge of the temporal lobe to the hippocampus, a zone of the cerebrum that is important particularly for the formation of memory content. From an anatomical perspective, the entry channel to the hippocampus runs along a system of fibers in which electrical signals are transmitted to particular cell groups. The stimuli are sorted in the first cell group, passed on to the second, and then sent back to the temporal lobe. Stated in simplified terms, this is how information on the environment is prepared and stored for further processing.

But what happens to this circuit under epileptic conditions? Haas and her colleagues demonstrated that the signal from the hippocampus back to the temporal lobe – the last step – fails shortly after an epileptic reaction starts, whereas it remains intact on the path leading to the hippocampus. The researchers were surprised to discover that new synaptic contacts develop

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Freiburg, 22.04.2016

within this circuit and that the size and complexity of the synapses increase. These structural changes could lead to an increase in the transmission of signals and ultimately to an increased risk for seizures. In vitro studies confirmed the suspicion that one of the involved cell types is excited more strongly than normal in epileptic mice. The researchers assume that these cells might function as highly interconnected epileptic nodes in the hippocampus and that the excitatory circuit might cause pathological changes there in particular. “The issue is of special significance, because it is not yet entirely clear which factors in the hippocampus contribute to triggering epileptic seizures,” says Haas.

The team now plans to investigate the entire modified chain of signals between the temporal lobe and the hippocampus. In particular, they aim to study whether the boost in the entry signal is a cause or an effect of epileptic activity. The researchers are also interested in determining which molecular mechanisms form the basis of synaptic modifications. Further studies will presumably result in the discovery of new therapeutic or preventive strategies. For example, Haas sees therapeutic potential in the modification of the affected areas: “If we could reduce the excitation of the hippocampus, for instance by means of cell-specific genetic manipulation, it might be possible to decrease the severity of epilepsy and at the same time lower the side-effects of therapy. However, we need to conduct further research to achieve this ambitious goal.”

Original publication:

Janz P, Savanthrapadian S, Häussler U, Kiliass A, Nestel S, Kretz O, Kirsch M, Bartos M, Egert U, Haas CA (2016) Synaptic remodeling of entorhinal input contributes to an aberrant hippocampal network in temporal lobe epilepsy. *Cerebral Cortex*.

DOI: 10.1093/cercor/bhw093

URL:

<http://cercor.oxfordjournals.org/content/early/2016/04/12/cercor.bhw093.short?rss=1>

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