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Epilepsy changes brain architecture

Epileptic fits, i. e. abnormal excessive neuronal activity in the hippocampus, severely affects nerve cells and can lead to permanent damage. A team of researchers led by Prof. Dr. Carola Haas from the Neurocenter at the University of Freiburg is focusing on changes in the brain anatomy of patients suffering from temporal lobe epilepsy as well as on the molecular and cellular processes underlying the disease. The team's research focuses on stem cells, granule cell dispersion and the molecule Reelin, which helps migrating neurons reach their proper destination.

Spatial relationships between groups of neurons in the brain are always of functional relevance. However, defective function is not always recognisable from changes in the cell architecture. The term epilepsy refers to a diverse set of symptoms related to the abnormal synchronisation of different brain areas. Temporal lobe epilepsy, which is associated with distinctive pathological structural changes in the brain, spreads from one or both temporal lobes of the brain and leads to recurrent epileptic seizures. Temporal lobe epilepsies, which cannot be treated adequately with medication, mainly arise in the hippocampus. "As the disease progresses, more and more neurons die, the ordered architecture of the different cell types disappears, leading to the scarring of the affected tissue," said Prof. Dr. Carola Haas from the Neurocenter at the University of Freiburg.

Guides for migrating cells

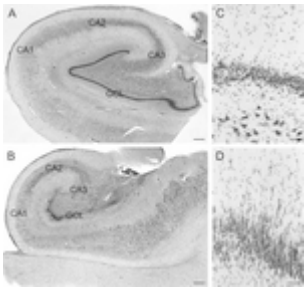


Photo of healthy human hippocampus (top left) showing a magnified band of granule cells in the dentate gyrus (top

Haas and her team have observed that temporal lobe epilepsies gradually lead to changes in the architecture of a specific hippocampal cell layer. This phenomenon, in which the granule cells in the hippocampal dentate gyrus region lose their dense packing and migrate away from their normal position, is referred to as granule cell dispersion. Although little is still known about the consequences of such dispersions, researchers have found that dispersion protects the dentate gyrus cells effectively against neuronal overexcitation associated with an epileptic seizure; other neuronal cell types die. "As epileptologists and neurobiologists we are particularly interested in the reasons why such architectural changes occur," Haas said.

The researchers became interested in the phenomenon of granule cell dispersion a couple of years ago when they discovered a mouse mutant with a defective Reelin gene. Mice that lack Reelin proteins are characterised by architectural changes in the brain that are similar to

right); sclerotic human hippocampus (bottom left) characterised by the dispersion of granule cells (bottom right). (© Prof. Dr. Carola Haas)

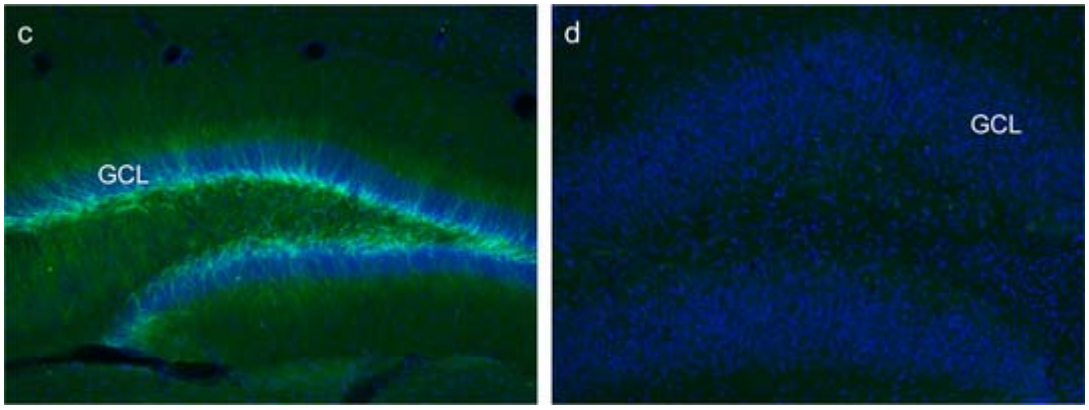
those that occur in epilepsy patients, including the disorganisation of cortical laminar layers in the central nervous system.

Reelin plays an important role in early development. It is now known that Reelin helps regulate neuronal migration and positioning in the developing brain. If the protein is not secreted by the initial neurons, the neurons that subsequently develop do not know in which layer of the brain they have to stop migrating. It is thus impossible for the correct architecture to form. “We were able to show in mice that the lack of Reelin also leads to the abnormal alignment of the granule cells in the hippocampus. This has an effect similar to that observed in people with temporal lobe epilepsies,” Haas said. In 2002, Haas and her team examined hippocampal tissue removed from epilepsy patients during surgery. They found that these tissue samples lacked Reelin. “We now believe that epilepsy leads to Reelin deficiency,” Haas explained, going on to add, “and this then seems to lead to structural changes in the granule cell layer and other regions.”

Neurogenesis and protection against thunderstorms in the brain

After Haas and her team of researchers discovered a connection between epileptic seizures and Reelin deficiency, they conducted systematic studies in mouse models and cell cultures in which they used ion channel drugs to simulate epileptic changes. This enabled them to identify a causal relationship between Reelin deficiency and epileptic seizures. Changes in the tissue of epileptic mice resulted in a lack of Reelin and eventually in the dispersion of granule cells in the hippocampus.

The silencing of Reelin in mouse brains using antibodies also led to the dispersion of granule cells. The researchers from Freiburg have just concluded an experiment in which they examined the migration behaviour of granule cells in epileptic hippocampal tissue using confocal microscopes. They found that artificially induced epilepsy caused granule cells to leave their normal site and move through the tissue.



Mouse hippocampus seen under the fluorescence microscope: young granule cells (stained green) suggest the generation of neurons from progenitor cells (neurogenesis; left). Neurogenesis does not occur in epileptic brains (lack of green stain); instead, the nuclei of granule cells disperse (blue). (© Prof. Dr. Carola Haas)

Haas and her team are currently focused on elucidating the molecular mechanisms underlying epileptic changes in the mouse brain that lead to Reelin deficiency. They are also interested in the process of neurogenesis during epileptic seizures, as research suggests that brain areas with high epileptic activity are also the sites with the largest number of young neurons. What links are there between stem cell activity and epilepsy? Haas and her team are also involved in the new BrainLinks-BrainTools cluster of excellence at the University of Freiburg, which brings together

basic neurobiological research, clinical research and the emerging field of neurotechnology.

Haas and her team envisage that their research will eventually contribute to developing methods involving the targeted application of drugs or the use of brain implants that will help to bring the chaos in the brains of epilepsy patients under control. The team also has a strong interest in the development of a new generation of electrode systems and imaging techniques. A recent paper published by the Freiburg group and their cooperation partners reports on the beneficial effects of astrocytes, a specific type of hippocampal glial cells. They found that astrocytes help reduce long-term damage brought on by epileptic fits. Further studies are needed in order to substantiate the finding that astrocytes have this protective influence. However, the researchers' findings suggest that it might eventually be possible to bring the electrical thunderstorms in the brain under control.

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A contribution from:

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