New findings on memory impairment in epilepsy

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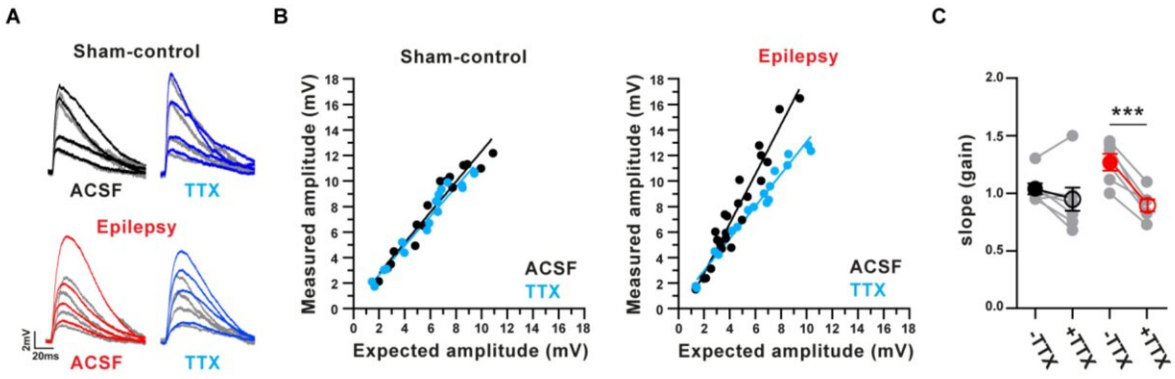

Effects of TTX on EPSP summation in linearly integrating 1st order CA1 pyramidal neuron dendrites. A, Examples of compound uEPSPs in sham-control and epileptic CA1 pyramidal cells. Gray lines indicate traces derived from arithmetic summation of single-spine EPSPs and represent compound EPSPs that would be obtained with purely linear summation. In epileptic mice, measured compound EPSPs were larger than expected from linear summation. B, Plotting measured EPSPs vs. EPSP sizes expected from arithmetic summation in ACSF and following application of 500 nM tetrodotoxin (TTX). The slope of the fitted line describing summation is reduced in epileptic, but not in control animals. C, Quantification of linear summation, and the TTX effects (sham-control and epileptic n=7 and 6, respectively, 2-way repeated measures ANOVA main effect, shamcontrol vs. epileptic: $F(1\ 11)=0.88$, $p=0.37$; ACSF vs. TTX: $F(1\ 11)=26.96$, $p=0.0003$; interaction: $F(1\ 11)=10.15$, $p=0.0087$; Asterisks indicate Bonferroni´s post-test, ACSF vs. TTX in epileptic $p=0.0003$). No effect of TTX on uEPSP peak amplitude, uEPSP rise time, and uEPSP decay time constant was detected (two-way repeated measures ANOVA n.s. for all parameters). Credit: *Brain* (2022). DOI: 10.1093/brain/awac455

People with chronic epilepsy often experience impaired memory. Researchers at the University of Bonn have now found a mechanism in mice that could explain these deficits. The German Center for Neurodegenerative Diseases (DZNE) was also involved in the study. The results are published in the journal *Brain*, but a preliminary version is already available online.

Suppose you go to visit an acquaintance you have not been to see in a long time. Nevertheless, you ring the correct doorbell without hesitation: The apple tree in the front yard with the wooden birdhouse next to it, the bright red painted fence, the clinkered facade—all this signals that you are in the right place.

Each place has numerous characteristics that distinguish it and make it unmistakable as a whole. In order to remember a place, we therefore need to store the combination of these features (this can also include sounds or smells). Because only then can we confidently recognize it when we visit it again, and tell it apart from similar places.

It is possible that this retention of the exact combination of features is impaired in people with chronic epilepsy. At least the findings of the current study point in this direction. "In the study, we looked at neurons in the hippocampus of mice," explains neuroscientist Dr. Nicola Masala of the Institute of Experimental Epileptology and Cognitive Sciences at the University Hospital Bonn.

Specific neurons fire when a place is visited

The hippocampus is a region in the brain that plays a central role in memory processes. This is especially true for spatial memory: "In the hippocampus there are so-called place cells," Masala says. "These help

us remember places we have visited." There are about one million different place cells in the mouse hippocampus. And each responds to a combination of specific environmental characteristics. So, to put it simply, there is also a place cell for "apple tree/birdhouse/fence".

But how is it ensured that the place cell only responds to a combination of these three features? This is ensured by a mechanism known as "dendritic integration". Because place cells have long extensions, the dendrites. These are dotted with numerous contact points where the information that the senses convey to us about a place is received (de facto, there are often hundreds or thousands of them). These contacts are called synapses.

When signals arrive at many neighboring synapses at the same time, a strong voltage pulse may form in the dendrite—a so-called dendritic spike.

In this way, the dendrite integrates different types of location information. Only when they all come together it may generate a spike. And only then is this combination stored, so that we recognize the house of our acquaintance the next time we visit it.

"In mice with epilepsy, however, this process is impaired," explains Prof. Dr. Heinz Beck, in whose research group Dr. Masala did her doctorate and who is also speaker of the Transdisciplinary Research Area "Life and Health" at the University of Bonn. "In them, the spikes already occur when only a few synapses are stimulated. Nor does the stimulation have to occur at exactly the same time."

The place cells of the sick rodents do not look so carefully. They fire at all the houses with an apple tree in the front yard. As a result, the information stored is less specific. "We were able to show in our experiments that the affected animals had significantly greater problems

distinguishing familiar places from unfamiliar ones," Masala points out.

Active substances improve memory

But what is the reason for this? For a spike to form, large amounts of electrically charged particles (the ions) must flow into the cell. For this purpose, pores open in the membrane that surrounds the dendrite—the ion channels.

"In our lab animals, a special channel for sodium ions was significantly more prevalent than normal in the dendrite membrane," Dr. Tony Kelly of the Institute of Experimental Epileptology and Cognitive Sciences, who co-supervised the study, explains. "This means that just a few poorly synchronized stimuli at the synapses are enough to open many channels and elicit a spike."

There are inhibitors that very specifically block the affected channel, preventing the influx of sodium ions. "We administered such a substance to the animals," Masala says. "This normalized the firing behavior of their dendrites. They were also better able to remember places they had visited."

The study thus provides insight into the processes involved in memory retrieval. In addition, in the medium term it gives rise to hopes of producing new drugs that can be used to improve the memory of epilepsy patients. These promising results are also the result of fruitful cooperation. "Without the collaboration especially with the laboratories of Prof. Dr. Sandra Blaess, Prof. Dr. Laura Ewell and Prof. Dr. Christian Henneberger at the University of Bonn, this success would not have been possible," Masala says.

More information: Nicola Masala et al, Targeting aberrant dendritic integration to treat cognitive comorbidities of epilepsy, *Brain* (2022).

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