Tracking down leaks in the blood-brain barrier

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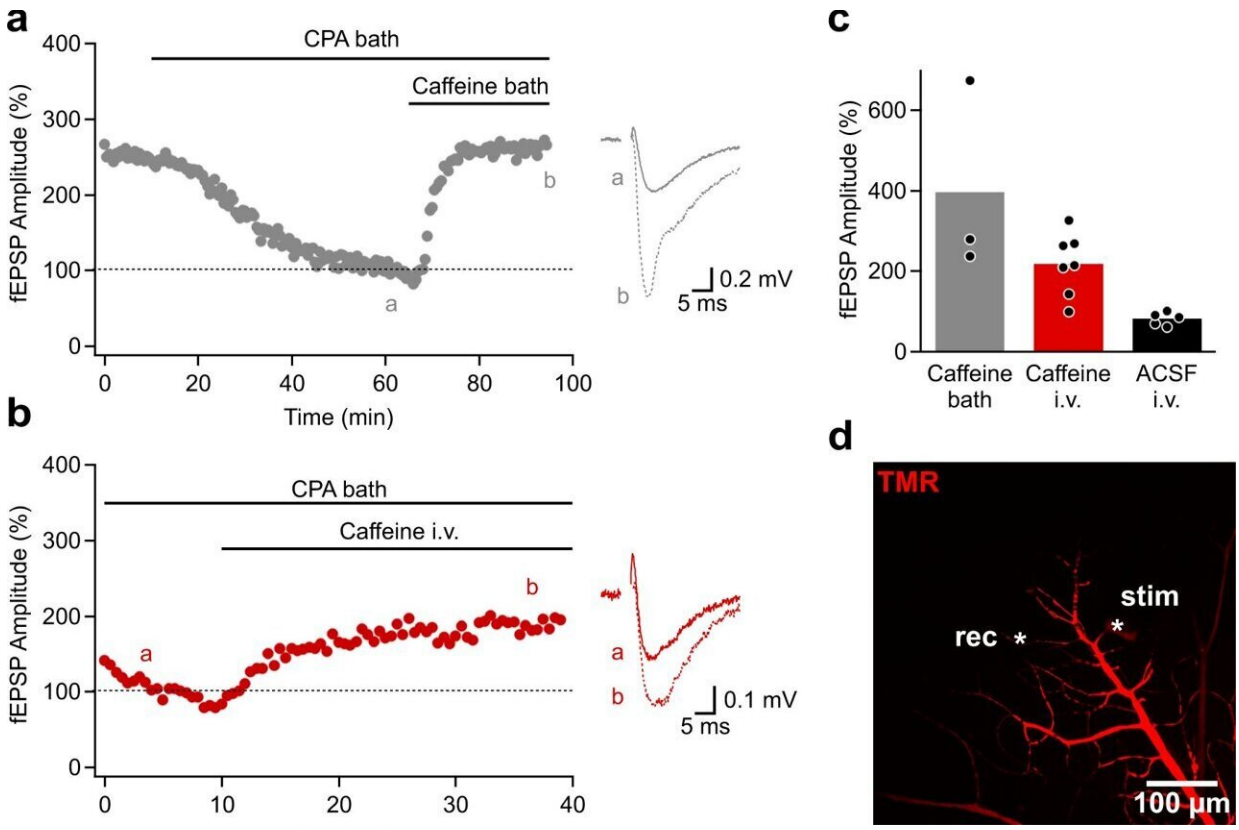

Monitoring the pharmacological effect on neuronal responses after drug passage through the BBB. a Time course of an example experiment of fEPSP recordings in the hippocampal area CA1. The adenosine A1-receptor CPA reduces synaptic responses. This effect is antagonized by co-application of caffeine. Inset shows recordings (average of 5 traces) from times indicated by lower case letters. b Top panel: Intravascular (i.v.) application of caffeine also antagonizes the effect of CPA (pre-applied) and increases synaptic responses. Note the different time scale of the x-axis when compared to a). Bottom panel: Control intravascular

injection of ACSF does not alter synaptic responses. c Summary of percentage fEPSP amplitude changes after caffeine bath application (n = 3 from 2 injections/2 mice), intravascular caffeine application (n = 5 from 3 injections/4 mice) and intravascular ACSF application (n = 5 from 3 injections/3 mice). Bar graph shows mean ± SEM. d MIPs of caffeine (top) and sACSF (bottom) injected vascular tree. The asterisks denote the positions of the stimulating (stim) and recording (rec) pipettes. Images are representative of 10 experiments. Credit: *Nature Communications* (2023). DOI: 10.1038/s41467-023-36070-6

In epilepsy research, it has long been assumed that a leaky blood-brain barrier is a cause of inflammation in the brain. Using a novel method, researchers from Bonn University Hospital (UKB) and the University of Bonn have demonstrated that the barrier between the blood and the central nervous system remains largely intact. The approach used in their study provides important insights into the development of epilepsy and could significantly optimize drug development in the pharmaceutical industry. The study results have recently been published in the journal *Nature Communications*.

500 kilometers of vessels in the human brain are lined with ten square meters of thin cell layer—the blood-brain barrier (BBB). This barrier protects the brain against harmful substances as well as pathogens. It also links the brain to the other organs in the body. If this selective barrier is leaky, diseases such as Parkinson's, multiple sclerosis, Alzheimer's could develop. Malfunctions of the BBB also play an important role in brain tumors.

Researchers at the UKB and the University of Bonn want to get to the bottom of these interactions. To study BBB transport at the cellular level, they developed micropipette-based local perfusion of capillaries, i.e., the finest blood vessels, in acute brain slices and combined it with multiphoton microscopy.

Prof. Dirk Dietrich, head of the experimental neurosurgery section at the Clinic of Neurosurgery at the UKB, compares the new analysis technique of the blood-brain barrier investigated in the study to a flat bicycle tire. "If the tire loses air, you don't know where the leak is. That's why you hold the inflated bicycle tube under water to identify the leak. This principle also underlies our method." The researchers use a micropipette to fill the microscopic blood vessels with a liquid from the inside. Leaks are then visible to them under the multiphoton microscope.

His colleague Alf Lamprecht, professor of pharmaceutical technology and biopharmacy at the Pharmaceutical Institute of the University of Bonn, hopes that the new method could advance early drug development. "When a new active ingredient is developed, the question always arises as to whether and, above all, how it passes the blood-brain barrier. Identifying these transport mechanisms and barriers is enormously important for making the drug available in the brain."

The results of the current study have potential to solve this problem in pharmacy. First author of the published article Dr. Amira Hanafy, a postdoctoral fellow at UKB's Clinic of Neurosurgery, says, "With the method we developed, we have a good tool to evaluate whether active ingredients reach the brain."

More information: Amira Sayed Hanafy et al, Subcellular analysis of blood-brain barrier function by micro-impalement of vessels in acute brain slices, *Nature Communications* (2023). DOI: 10.1038/s41467-023-36070-6

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