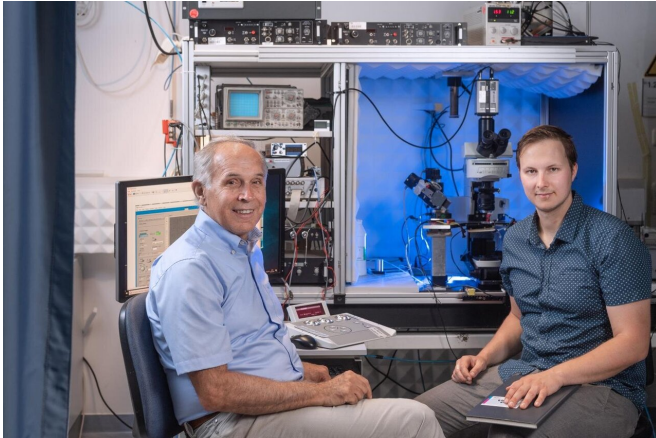


Direct toxic action of beta-amyloid identified

9 August 2019



Arthur Konnerth (left) and Benedikt Zott in front of the experimental setup. Credit: Andreas Heddergott / TUM

Hyperactive neurons in specific areas of the brain are believed to be an early perturbation in Alzheimer's disease. For the first time, a team from the Technical University of Munich (TUM) was able to explain the reasons and mechanisms underlying this early and therefore important neuronal dysfunction. They found that the excitatory neurotransmitter glutamate persists for too long near active neurons. This causes a pathological overstimulation of those neurons—most likely contributing critically to impaired learning and memory loss in Alzheimer's patients.

The brains of Alzheimer's patients who have already developed clinical symptoms contain large clumps of the protein beta-amyloid, known as plaques. Many therapeutic approaches focus on removing plaques, but such attempts have met with only limited success to date.

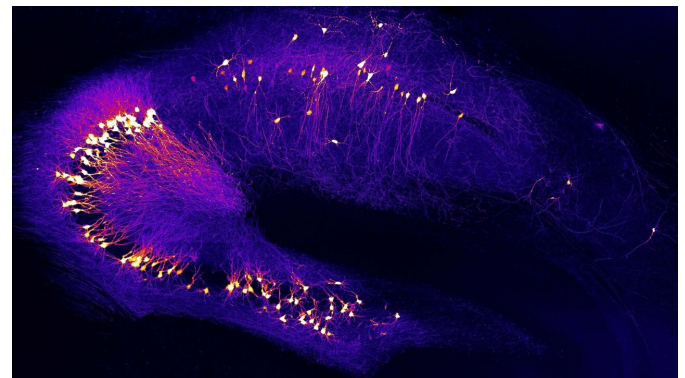
"It's crucial that we detect and treat the disease much earlier. We therefore focused on hyperactive neurons, which occur at a very early stage—long before patients develop [memory loss](#)," explains Professor Arthur Konnerth, Hertie Senior Professor of Neuroscience at the TUM. As a consequence of

hyperactivation, connected neurons in the circuits constantly receive false signals, leading to impairments in signal processing.

Together with his doctoral student Benedikt Zott and the entire research team, Konnerth succeeded in identifying the cause and trigger of this early disturbance in the brain. The discovery may open the way to new therapeutic approaches. The study appeared in the journal *Science*.

Beta-amyloid blocks glutamate re-uptake

Neurons use chemicals called neurotransmitters to communicate with each other. Glutamate, one of the most important of these chemicals, serves to activate connected neurons. Glutamate is released at the connecting site between two neurons, called synapse, and then rapidly removed to allow the transmission of the next signal. This removal involves so-called active pump molecules as well as a passive transport of [glutamate](#) along nearby membranes.



Neurons in the hippocampus, a brain region for learning and memory, that is impaired already at early stages of Alzheimer's disease. Credit: Y. Zhang und A. Konnerth / TUM

The researchers discovered that high concentrations of glutamate persisted too long in

the synaptic cleft of hyperactive [neurons](#). This was due to the action of beta-amyloid molecules, which blocked glutamate transport out of the synaptic cleft. The team tested the mechanism using beta-amyloid molecules from patient samples and by using various mouse models obtaining similar results with both approaches.

Indication for treatment strategies at early stages

The team was also intrigued to discover that the neurotransmitter blockade was mediated by an early soluble form of beta-amyloid and not by the plaques. Beta-amyloid occurs initially as a single molecule form, or monomer, and then aggregates to double-molecule forms ([dimers](#)) and larger chains resulting, eventually, in plaques. The researchers found that glutamate blockade is caused by the soluble dimers.

"Our data provide clear evidence for a rapid and direct toxic effect of a particular [beta-amyloid](#) type, the dimers. We were even able to explain this mechanism," as Benedict Zott, first author of the study, outlined. The researchers now want to use this knowledge to further improve their understanding of the cellular mechanisms of Alzheimer's and, thus, to support the development of strategies for treatment at early stages of the disease.

More information: Benedikt Zott et al, A vicious cycle of β amyloid–dependent neuronal hyperactivation, *Science* (2019). [DOI: 10.1126/science.aay0198](#)

Provided by Technical University Munich

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