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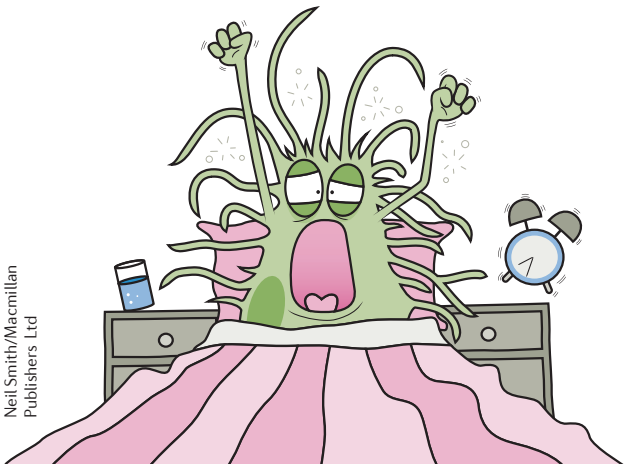
NEURON—GLIA INTERACTIONS

Waking the synapse

> when α7nAChRs were deleted specifically in astrocytes, activity-related oscillations in D-serine availability were abolished

The responsiveness of astrocytes to neuromodulators, coupled with their ability to influence neuronal activity through the release of 'gliotransmitters', suggests that they could translate information about brain states to the neurons with which they interact. In this study, Haydon and colleagues reveal a mechanism through which astrocytes can gate synaptic function in the mouse hippocampus in response to fluctuations in wakefulness.

Hippocampal synaptic function can be modulated by the availability of the NMDA receptor (NMDAR) co-agonist D-serine, a gliotransmitter that is released by astrocytes. To determine the effects of brain state on D-serine availability, the authors collected hippocampal slices from mice at different times of the day and used electrophysiology to assess the D-serine 'saturation index', which corresponds to the occupancy of the NMDAR co-agonist binding site and thus to D-serine availability. The saturation index was highest at the end of the animals' active (dark) phase and gradually reduced during the rest (light) phase. These daily oscillations in D-serine availability were abolished in mice in which astrocytic gliotransmitter release was impaired.



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The authors confirmed that the D-serine fluctuations were driven by changes in activity and/or wakefulness by showing that enforced wakefulness during the rest phase increased the D-serine saturation index and that *in vivo* hippocampal D-serine concentrations measured using microdialysis correlated with the animal's level of locomotor activity as assessed from video recordings. They also assessed the influence of the D-serine oscillations on behaviour and found that mice exhibited better contextual fear memory when training took place during active (high-D-serine) periods than when they trained during rest periods.

The effects of wakefulness on brain activity are driven by cholinergic projections from the septum to the cortex. Astrocytes express several types of acetylcholine receptor (AChR), suggesting that brain state-dependent changes in cholinergic activity could influence astrocytic D-serine synthesis and/or release. Indeed, the authors showed that treating hippocampal slices taken from animals during rest with an AChR agonist increased the D-serine saturation index, whereas α7-nicotinic AChR (α7nAChR) antagonists reduced the saturation index in slices collected during active periods. Furthermore, when α7nAChRs were deleted specifically in astrocytes, activity-related oscillations in D-serine availability were abolished altogether. Finally, optogenetic stimulation of acetylcholine release boosted NMDAR-dependent synaptic activity in an α7nAChR-dependent manner.

These findings demonstrate that, by 'sensing' changes in cholinergic tone and translating them into alterations in D-serine availability, astrocytes can shape synaptic function in response to fluctuations in wakefulness. Building on this work by investigating the intracellular pathways through which α7nAChR-mediated signalling alters astrocytic gliotransmission may provide new avenues for the development of therapeutics for disorders, such as schizophrenia, that are associated with altered cholinergic activity or NMDAR malfunction.

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ORIGINAL ARTICLE Papouin, T. *et al.* Septal cholinergic neuromodulation tunes the astrocyte-dependent gating of hippocampal NMDA receptors to wakefulness. *Neuron* http://dx.doi.org/10.1016/j.neuron.2017.04.021 (2017)