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GLIA

Astrocytic go-betweens

> Light-induced activation of the septal cholinergic neurons induced rapid, temporary increases in calcium concentration in these astrocytes.

The release of acetylcholine (ACh) from septal neurons that project to the hippocampus is thought to have a key role in hippocampal learning and memory formation, but the mechanism by which ACh exerts its effects on hippocampal circuitry has been unclear. Now, Beck and colleagues show that ACh released by septal projection neurons activates glutamate-releasing astrocytes in the hilus, which in turn activate GABAergic hilar interneurons, resulting in inhibition of dentate gyrus granule cells in the hippocampus.

To determine the targets of ACh transmission, the authors first expressed channelrhodopsin 2 (ChR2) in septal cholinergic neurons in anaesthetized mice. Subsequent *in vivo* patch-clamp recordings revealed that light stimulation of these cells induced the hyperpolarization and hence inhibition of granule cells. In hippocampal slices, application of methyllycaconitine (MLA), an antagonist of nicotinic ACh receptors, blocked this light-induced inhibition of the granule cells, indicating that the inhibition is ACh-dependent.


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It had been proposed previously that ACh from septal neurons excites GABAergic hilar interneurons, which in turn inhibit the granule cells. In support of this idea, the authors found that light stimulation of cholinergic septal neurons induced an increase in activity in fast-spiking putative hilar interneurons, as revealed using *in vivo* silicon probe recordings. Moreover, in hippocampal slices, similar increases in light-induced hilar interneuronal activity preceded the depolarization of granule cells and could be reduced in magnitude through the application of MLA.

The authors next examined whether septal cholinergic neurons directly activate hilar interneurons. In an attempt to isolate ACh-evoked excitatory postsynaptic potentials in hilar interneurons, the authors blocked ionotropic glutamate receptor responses in these cells. Strikingly, however, this blocked responses in hilar interneurons to optogenetic activation of septal cholinergic neurons, suggesting that the latter may confer their effects on these interneurons via glutamate-releasing cells.

Other studies have provided evidence that ACh-induced glutamate release from glia can mediate delayed excitatory neurotransmission, so the authors examined whether hilar astrocytes act to relay the septal neuron signal. Light-induced activation of the septal cholinergic neurons induced rapid, temporary increases in calcium concentration in these astrocytes. Moreover, in hippocampal slices, application of an inhibitor of glial metabolism disrupted granule cell inhibition following light-induced activation of septal cholinergic neurons. Finally, targeted application of a calcium chelator to hilar astrocytes also reduced granule cell inhibition following light stimulation and led to a decrease in the light-induced excitation of hilar interneurons, suggesting that astrocyte activation has a key role within this circuit.

Together, these findings describe a means by which ACh exerts its role in memory encoding in the hippocampus and, in doing so, highlight an important role for astrocytes in this signalling process.

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