

Combining Multielectrode Recording and Opto-genetic Control of Hippocampal Neurons in Awake, Behaving Rats.

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Synaptic plasticity in the hippocampus is thought to be responsible for the acquisition of new semantic and episodic memories. In rat hippocampus, artificially induced LTP interferes with spatial learning and learning interferes with the ability to potentiate synapses artificially. Current approaches for probing synaptic plasticity within and between regions of the hippocampus rely on electrical stimulation, which presumably activates both excitatory principal cells and inhibitory interneurons. In addition to this lack of specificity, electrical stimulation induces artifacts that make simultaneous recording of neural activity during and immediately following stimulation difficult. Viral transfection of the light-sensitive ion channel, channelrhodopsin-2 (ChR-2), combined with in-vivo light delivery, provides an elegant method for selectively activating particular classes of cells without electrical artifacts.

We have developed a combined multi-electrode/fiber optic system that allows us to selectively activate principal cells in the hippocampus of an awake, behaving animal following infection with a lentivirus expressing ChR-2 under the *CaMKII α* promoter. Using this system, we can record field potentials and isolated individual units during optical stimulation of excitatory neurons. After transfecting cells and recording activity in area CA1, we could reliably evoke a population response with light pulses as short as 2 ms. Furthermore, in contrast to in vitro experiments [1], we evoked this response with a short latency of about 5 ms. Additionally, we found that simultaneously recorded neurons were silenced for about 20 ms following the evoked population response, indicating that this technique can be used to briefly interfere with ongoing activity.

Following transfection of cells in CA3 and the dentate gyrus and targeting CA3 with an optical fiber, we were able to evoke responses in both areas CA3 and CA1. We found that stimulation using a sequence of 5 ms optical pulses resulted in a frequency-dependent short-term facilitation of the population response. Specifically, the evoked local field potential following the second pulse in the sequence increased with increasing frequency to a maximum of about 30 Hz. This peak frequency is consistent with the previously reported characteristics of the ChR-2 ion channel [1]. Interestingly, the response of area CA3 to repeated pulses saturated more rapidly than in CA1; at 8Hz, maximal response was achieved after 3-4 pulses, but continued to rise in area CA1 for 8 pulses. These differences suggest that short term plasticity in CA3 recurrent collaterals has different properties than that at the CA3-CA1 synapse. The ability to selectively activate excitatory neurons and record the local and downstream effects offers a new and potentially very powerful tools for probing the properties of neural activity and plasticity in-vivo.

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References

[1] Millisecond-timescale, genetically targeted optical control of neural activity. E. S. Boyden, F. Zhang, E. Bamberg, G. Nagel, and K. Deisseroth, *Nature Neuroscience* 8(9):1263–1268, Sept. 2005.