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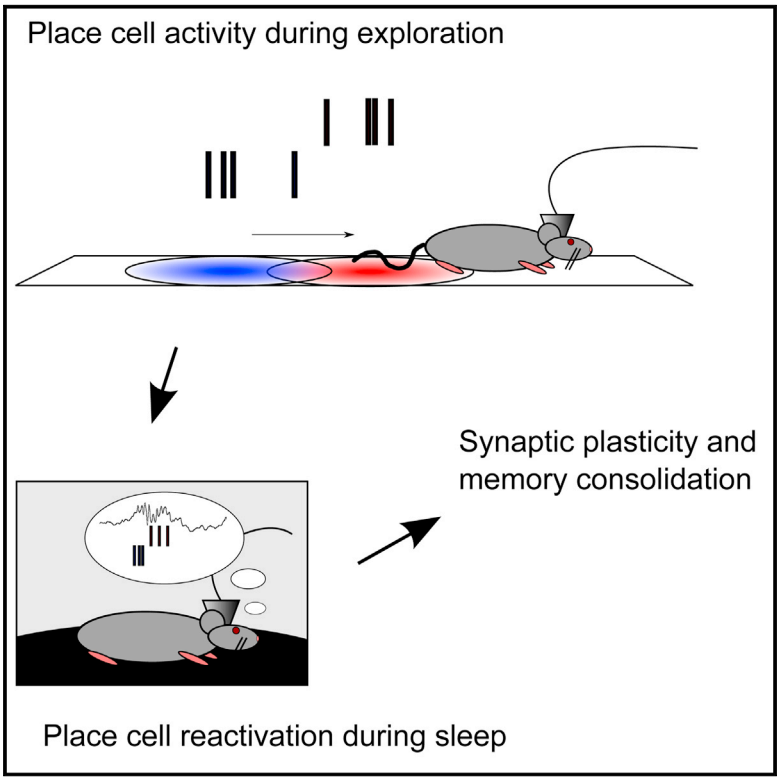
Sharp-Wave Ripples Orchestrate the Induction of Synaptic Plasticity during Reactivation of Place Cell Firing Patterns in the Hippocampus

Graphical Abstract



Highlights

- Reactivated place cell firing patterns can induce LTP in the hippocampus
- Sharp-wave ripples are required for the induction of LTP
- Dendritic depolarization during sharp-wave ripples is required for LTP
- The timing of place cell firing within sharp-wave ripples controls LTP induction

Authors

Josef H.L.P. Sadowski, Matthew W. Jones, Jack R. Mellor

Correspondence

matt.jones@bristol.ac.uk (M.W.J.), jack.mellor@bristol.ac.uk (J.R.M.)

In Brief

Sadowski et al. show that reactivation of neuronal firing patterns during sleep induces synaptic plasticity, providing a mechanism for the observation that memories are consolidated during sleep.

Sadowski et al., 2016, Cell Reports *14*, 1916–1929
March 1, 2016
http://dx.doi.org/10.1016/j.celrep.2016.01.061

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Sharp-Wave Ripples Orchestrate the Induction of Synaptic Plasticity during Reactivation of Place Cell Firing Patterns in the Hippocampus

Josef H.L.P. Sadowski,[1] Matthew W. Jones,[1,2,*] and Jack R. Mellor[1,2,*]
[1]Centre for Synaptic Plasticity, School of Physiology, Pharmacology and Neuroscience, University of Bristol, University Walk, Bristol BS8 1TD, UK
[2]Co-senior author
*Correspondence: matt.jones@bristol.ac.uk (M.W.J.), jack.mellor@bristol.ac.uk (J.R.M.)
http://dx.doi.org/10.1016/j.celrep.2016.01.061

SUMMARY

Place cell firing patterns reactivated during hippocampal sharp-wave ripples (SWRs) in rest or sleep are thought to induce synaptic plasticity and thereby promote the consolidation of recently encoded information. However, the capacity of reactivated spike trains to induce plasticity has not been directly tested. Here, we show that reactivated place cell firing patterns simultaneously recorded from CA3 and CA1 of rat dorsal hippocampus are able to induce long-term potentiation (LTP) at synapses between CA3 and CA1 cells but only if accompanied by SWR-associated synaptic activity and resulting dendritic depolarization. In addition, we show that the precise timing of coincident CA3 and CA1 place cell spikes in relation to SWR onset is critical for the induction of LTP and predictive of plasticity generated by reactivation. Our findings confirm an important role for SWRs in triggering and tuning plasticity processes that underlie memory consolidation in the hippocampus during rest or sleep.

INTRODUCTION

Synaptic plasticity is believed to mediate the encoding of memories by strengthening connectivity between co-active neurons representing constituent features of an event or environment (Hebb, 1949; Bliss and Collingridge, 1993). Recently encoded memories are liable to interference and require consolidation, a process thought to occur during rest and sleep when recently active neural ensembles are reactivated in the hippocampus (Pavlides and Winson, 1989; Wilson and McNaughton, 1994; Skaggs et al., 1996; Louie and Wilson, 2001; Lee and Wilson, 2002; Foster and Wilson, 2006; Diba and Buzsáki, 2007). During these consolidation epochs, existing hippocampal connectivity may be refined through further plasticity and consolidated engrams subsequently integrated into neocortex for longer-term storage (Frankland and Bontempi, 2005). This two-step model of memory formation therefore requires that long-term potentiation (LTP) is induced during both the encoding and consolidation stages (Buzsáki, 1989).

LTP can be induced at hippocampal synapses by intense, high-frequency stimulation of presynaptic axons, postsynaptic depolarization coupled with presynaptic stimulation (Bliss and Collingridge, 1993), or by delivering tightly synchronized pre- and postsynaptic activity (Magee and Johnston, 1997; Bi and Poo, 1998; Debanne et al., 1998; Buchanan and Mellor, 2010). The latter, also referred to as spike-timing-dependent plasticity (STDP), leads to LTP or long-term depression (LTD) according to the precise timing and temporal order of pre- and postsynaptic activity. Spike-timing-dependent LTP (STD-LTP) requires causal spiking to occur within a narrow temporal window, with a presynaptic spike followed by a postsynaptic spike within 30 ms. Anti-causal activity, whereby the postsynaptic neuron fires before the presynaptic neuron, can lead to STD-LTD. However, STDP rules are synapse- and developmental-stage-specific. For example, at mature Schaffer collateral (SC)-CA1 synapses, multiple postsynaptic spikes are required for STD-LTP (Pike et al., 1999; Buchanan and Mellor, 2007); this is important when considering the spiking requirements for STDP between co-active neurons encoding a given memory. *In vivo*, tightly correlated CA1 and CA3 pyramidal cell spiking is predicted to satisfy the requirements for STDP induction at SC-CA-1 synapses (O'Neill et al., 2010). Indeed, there are defined periods during the encoding and consolidation phases of hippocampal memory processing when CA1 and CA3 pyramidal cells are coactive and STDP may occur (Isaac et al., 2009; Bush et al., 2010a; Carr et al., 2011; Sadowski et al., 2011).

Hippocampal place cells fire in a location-dependent manner (O'Keefe and Dostrovsky, 1971), and thousands of cells in the hippocampal CA3-CA1 network are likely to have overlapping place fields, and therefore be co-activated, within a given environment (Muller et al., 1987). The firing patterns of cells with overlapping place fields may satisfy the requirements for STDP to be induced during memory encoding, for example on exploration of a novel environment (Muller et al., 1996). In fact, these firing patterns have been shown to induce LTP at SC-CA1 synapses *in vitro*, but only when cholinergic receptors are also activated in a manner that may mimic the elevated cholinergic tone observed during awake behavior (Isaac et al., 2009). This is consistent with previous evidence for induction