This Week in The Journal

How Sensory Input During Sleep Enhances Memory

Yina Wei, Giri P Krishnan, Lisa Marshall, Thomas Martinetz, and Maxim Bazhenov

(see pages 811–824)

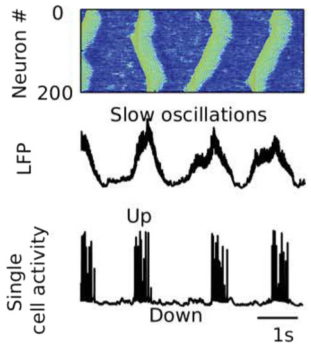
Memories for significant events are strengthened during subsequent slow-wave sleep, possibly through the reactivation of neural circuits encoding the initial event. Remarkably, memory consolidation during sleep can be potentiated by presenting brief sensory stimuli at specific phases of slow oscillations. To learn how such enhancement might occur, Wei et al. constructed a computational model of the thalamocortical network with physiologically appropriate synaptic connections, intrinsic ionic conductances, and spike timing-dependent synaptic plasticity.

To simulate learning, five small populations of pyramidal neurons were activated in a particular sequence, sometimes preceded by simulated sensory input to the first population. After this training, memory was assessed by examining both the strength of synapses between the activated populations and the extent to which activating the first population led to activation of the complete trained sequence. By both measures, memories formed during training.

Next, the authors altered the ionic conductances of neurons to mimic the effects of sleep-regulating neuromodulators. This caused the mean membrane potential of cortical excitatory neurons to oscillate, simulating the local field potential oscillations of slow-wave sleep. In some cases, simulated sensory input was delivered at particular phases of this slow oscillation. The ionic conductances were then returned to the initial state and memory was tested as it had been before.

Both synaptic strength and the ability of the model to reproduce the trained sequence were increased after simulated sleep, and both could be further enhanced by sensory input. This input was most effective when given near the end of a DOWN state, when it was most likely to generate an UP state; input failed to enhance memory when given during an ongoing UP state. Importantly, UP states triggered by sensory input frequently emerged in the neuronal population activated first during training, and then propagated through the remainder of the trained sequence. In contrast, UP states not preceded by a cue often began in other neuronal populations.

These results suggest that sensory cues presented during slow-wave sleep enhance memories by increasing the likelihood that neural populations encoding a previous experience will be reactivated in the same pattern during sleep. This reactivation likely strengthens the activated synapses, thus facilitating pattern completion during subsequent testing.



A thalamocortical model mimicked slow-wave sleep, with oscillations in membrane voltage propagating across the population (heat map, top). Mean membrane potential of cortical neurons (middle) showed oscillations similar to those in slow-wave sleep, and individual neurons exhibited typical UP and DOWN states (bottom). See Wei et al. for details.

Contribution of PSA-NCAM to Antidepressant Actions

Jun Yamada, Chihiro Sato, Kohtarou Konno, Masahiko Watanabe, and Shozo Jinno

(see pages 825–842)

Neural cell adhesion molecule (NCAM) is an important regulator of nervous system development, with roles in neuron migration, axon guidance, and synaptogenesis. These functions are governed by the addition of long polysialic acid (PSA) chains that restrict the interactions of NCAM with other proteins. PSA-NCAM levels greatly decline in late developmental stages, but PSA-NCAM persists in some regions of the mature brain, including in neurogenic niches and in subsets of interneurons. The function of PSA-NCAM in interneurons is unclear, but it can modulate the effects of brain-derived neurotrophic factor and promote synaptic plasticity through interactions with AMPA receptors. Intriguingly, hippocampal PSA-NCAM levels are regulated by serotonin, and levels of PSA-NCAM are reduced in specific brain areas in people with depression and schizophrenia, both of which may stem from disruption of serotonergic signaling (Schnaar et al., 2014, Physiol Rev 94:461).

To elucidate the function of PSA-NCAM in mature hippocampus, Yamada et al. examined and manipulated its expression in mouse CA1. PSA-NCAM was expressed predominantly in interneurons that also expressed cholecystokinin (CCK) and vesicular glutamate transporter type 3 (VGluT3). Most $NCAM^+/VGluT3^+/CCK^+$ cells expressed serotonin 5-HT3a receptors and many were contacted by presynaptic boutons containing a marker of serotonergic terminals. In addition, many $NCAM^+/VGluT3^+/CCK^+$ cells expressed p11, a protein that enhances the surface expression of serotonin receptors and helps mediate the antidepressant effects of serotonin reuptake inhibitors like fluoxetine.

Restraint stress, which increases depression-related behaviors such as immobility in the forced swim test, reduced expression of p11 in CA1 CCK^+ cells, and reduced hippocampal levels of PSA-NCAM and ST8Sia-IV, a polysialyltransferase that synthesizes PSA. Treatment with fluoxetine reversed the behavioral effects of restraint stress and increased levels of p11, ST8Sia-IV, and PSA-NCAM. Importantly, hippocampal injection of an enzyme that digests PSA reduced p11 levels in unstressed mice, prevented fluoxetine-induced increases in p11 in stressed mice, and prevented fluoxetine-induced reductions in immobility in the forced swim test in both stressed and unstressed mice.

These results suggest that the expression of PSA-NCAM in a subset of CA1 interneurons contributes to the effects of antidepressants partly by allowing upregulation of p11. Learning how PSA-NCAM regulates p11 expression may suggest new avenues for treating depression and other conditions involving dysfunction of the serotonergic system.

This Week in The Journal was written by Teresa Esch, Ph.D.
https://doi.org/10.1523/JNEUROSCI.twij.40.4.2020.