Synaptic plasticity and hippocampal memory

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Synaptic plasticity as the neurophysiological substrate of learning

Hebb's Hypothesis (1949)
• Long-lasting change in the strength of the connections (‘synapses’) between neurons is the physiological basis of lasting memory.
• Synapses between neurons are strengthened when the neurons are active together: ‘neurons that fire together, wire together’.

Adapted from Fig. 24.4. in Bear, Connors, Paradiso (2014, 4th Ed) Neuroscience: exploring the brain.

Also compare Bast (2007, Rev Neurosci), Fig. 2, specifically focusing on hippocampal synaptic plasticity and its role in place learning.
Long-term potentiation (LTP) of hippocampal synapses

Entorhinal-hippocampal circuitry

Hippocampus

Schaffer collaterals

CA1

CA3

Dentate gyrus

Mossy fibres

Perforant path

Assciational/ commissural fibres

Temporoammonic path

Polymodal sensory inputs

Entorhinal cortex


LTP of perforant path-dentate gyrus synapses *in vivo*

LTP = sustained increase in the synaptic efficiency of a monosynaptic excitatory pathway caused by tetanic stimulation of the pathway, i.e. strong concurrent stimulation of a large proportion of the synaptic connections that make up the pathway (Bliss & Collingridge, 1993, *Nature*).

TVP Bliss & T Lomo (1973) *J. Physiol.* 232, 331-356
NMDA-type glutamate receptors are required to induce hippocampal LTP

For an *in vivo* demonstration of the selective contribution of NMDA receptors to LTP induction at perforant path dentate gyrus synapses see Bast et al. (2005, *J Neurosci*).
NMDA receptors and hippocampal LTP

**NMDA receptor activation by concurrent pre- and postsynaptic activation**

At resting potential:
- Glutamate, Mg^2+ blocks NMDA receptor
- AMPA receptor

During depolarization:
- Na^+ influx opens NMDA receptor
- Ca^2+ entry
- Mg^2+ expelled from channel

**NMDA receptors act as ‘coincidence’ detectors**

**AMPA receptors are required for both induction and expression of hippocampal LTP.**

Compare Fig. 25.8 and 25.9. in Bear, Connors, Paradiso (2014, 4th Ed) Neuroscience: exploring the brain
Blockade of hippocampal NMDA receptors blocks hippocampal LTP and hippocampal learning.

Tetanic stimulation

Distinct Contributions of Hippocampal NMDA and AMPA Receptors to Encoding and Retrieval of One-Trial Place Memory

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Allocentric place memory may serve to specify the context of events stored in human episodic memory. Recently, our laboratory demonstrated that, analogous to event-place associations in episodic memory, rats could associate, within one trial, a specific food flavor with an allocentrically defined place in an open arena. Encoding, but not retrieval, of such flavor-place associations required hippocampal NMDA receptors; retrieval depended on hippocampal AMPA receptors. This might have partly reflected the contributions of these receptors to encoding and retrieval of one-trial place, rather than flavor-place, memory. Therefore, the present study developed a food-reinforced arena paradigm to study encoding and retrieval of one-trial allocentric place memory in rats; memory relied on visuospatial information and declined with increasing retention delay, still being significant after 6 h, the longest delay tested (experiments 1 and 2). Hippocampal infusion of the NMDA receptor antagonist n-AP-5 blocked encoding without affecting retrieval; hippocampal infusion of the AMPA receptor antagonist CNQX impaired retrieval (experiment 3). Finally, we confirmed that the n-AP-5 infusions selectively blocked induction of long-term potentiation, a form of synaptic plasticity, whereas CNQX impaired fast excitatory transmission, at perforant-path dentate gyrus synapses in the dorsal hippocampus in vivo (experiment 4). Our results support that encoding, but not retrieval, of one-trial allocentric place memory requires the NMDA receptor-dependent induction of hippocampal synaptic plasticity, whereas retrieval depends on AMPA receptor-mediated fast excitatory hippocampal transmission. The contributions of hippocampal NMDA and AMPA receptors to one-trial allocentric place memory may be central to episodic memory and related episodic-like forms of memory in rats.

Key words: allocentric spatial learning; hippocampus; synaptic plasticity; NMDA; microinfusions; episodic-like memory
The Brain Prize for 2016 is awarded to Timothy Bliss, Graham Collingridge and Richard Morris for their ground-breaking research on the cellular and molecular basis of Long-Term Potentiation and the demonstration that this form of synaptic plasticity underpins spatial memory and learning.

http://www.thebrainprize.org/flx/prize_winners/the_brain_prize_winners_2016/
Which conclusion can we draw from the finding that selective blockade of hippocampal NMDA receptors selectively blocks hippocampal LTP and hippocampus-dependent place learning?

a) Hippocampal LTP-like synaptic plasticity is necessary for such learning.

b) Hippocampal LTP-like synaptic plasticity is sufficient for such learning.

c) Both a) and b).

d) None of the above.
Synaptic plasticity = memory?

Synaptic plasticity and memory (SPM) hypothesis
Learning is mediated by synaptic plasticity, i.e. synaptic plasticity is both necessary and sufficient for memory.

TABLE 1  Four formal criteria relevant to the assessment of the SPM hypothesis

| DETECTABILITY: If an animal displays memory of some previous experience, a change in synaptic efficacy should be detectable somewhere in its nervous system. |
| MIMICRY: Conversely, if it were possible to induce the same spatial pattern of synaptic weight changes artificially, the animal should display ‘apparent’ memory for some past experience which did not in practice occur. |
| ANTEROGRADE ALTERATION: Interventions that prevent the induction of synaptic weight changes during a learning experience should impair the animal’s memory of that experience. |
| RETROGRADE ALTERATION: Interventions that alter the spatial distribution of synaptic weights induced by a prior learning experience (see detectability) should alter the animal’s memory of that experience. |

For a recent review of evidence supporting the SPM hypothesis, see Takeuchi, Duskiewicz, Morris (2014, Phil. Trans. R. Soc. B).
Synaptic plasticity and hippocampal memory – selected reading

Textbook chapters
or


Reviews


Research papers

• What was Donald Hebb’s famous hypothesis on the physiological substrate of memories? How can it be used to explain memory?

• What is LTP and how is it demonstrated in vitro and in vivo?

• What are the roles of NMDA- and AMPA-type glutamate receptors in LTP?

• Which lines of evidence support that LTP-like synaptic plasticity mechanism mediate hippocampus-dependent learning and memory?

• Which criteria would need to be met to conclude that synaptic plasticity within a specific brain region, such as the hippocampus, is both necessary and sufficient for the memory representations supported by this brain region?