Synaptic plasticity and hippocampal memory

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Learning (‘encoding’) 

- External Stimulus
- Reciprocally connected neurons
- Concurrent activation of neurons: 
  - Neural representation of stimulus 
  - Strengthening of synapses
- Synaptic plasticity

Recall (‘retrieval’) 

- Recall cue
- Reciprocally connected neurons 
- Partial reactivation of neural ensemble by part of original stimulus 
- Strengthened synapses 
- Reactivation of complete neural ensemble through strengthened synapses

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
- Temporoammonic path
- Perforant path
- Mossy fibres
- Associational/commissural fibres

**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*).

Adapted from 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, Mg²⁺ blocks NMDA receptors.
- During depolarization, Na⁺ enters the channel, Mg²⁺ is expelled, and Ca²⁺ enters.

AMPARs 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

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 is necessary for such learning.

b) Hippocampal LTP is sufficient for such learning.

c) Both a) and b).

d) None of the above.
Synaptic plasticity and memory (SPM) hypothesis
Learning is mediated by synaptic plasticity, i.e. synaptic plasticity is both necessary and sufficient for memory.

For a recent review of evidence supporting the SPM hypothesis, see Takeuchi, Duskiewicz, Morris (2014, *Phil. Trans. R. Soc. B*).
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?