KING'S College LONDON

INSTITUTE OF PSYCHIATRY,
PSYCHOLOGY & NEUROSCIENCE

Module:
Biological Foundations of Mental Health

Week 4:
Biological basis of learning, memory and cognition

Professor
Peter Giese

Topic 1:

Learning, memory and synaptic plasticity

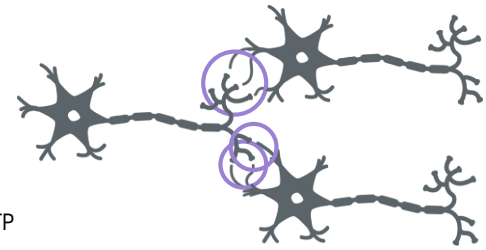
Part 4 of 4

Part 4

Part 4: Overview

In this section, we will:

- discuss the importance of LTP in the hippocampus in learning and memory
- learn about approaches to study whether LTP is induced through training in a memory task
- learn about methods that manipulate LTP and its impact on learning and memory



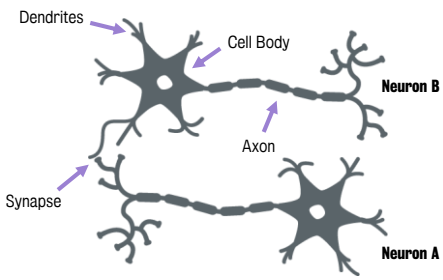
LTP:

- is connected to long lasting synaptic plasticity
- is input specific
- follows Hebb's postulate (Hebbian theory)

Is LTP a memory mechanism? (1)

Donald Hebb
Canadian psychologist

The Organization of Behaviour, 1949
This book illustrates the principle of how Hebb thought neurons behave when an animal learns new information



"When an axon of neuron A ... excite(s) neuron B and repeatedly or persistently takes part in firing it, some growth processes or metabolic changes take place in one or both neurons so that A's efficiency as one of the cells firing B is increased."

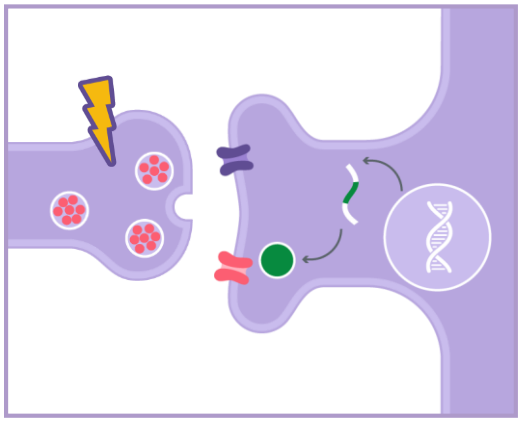
Although LTP follows Hebb's postulate, it is the **synaptic transmission that is enhanced** and not the firing.

Hebb (1949)

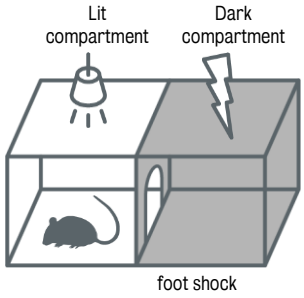
Is LTP a memory mechanism? (2)

Does such type of synaptic plasticity really exist in a behaving brain?

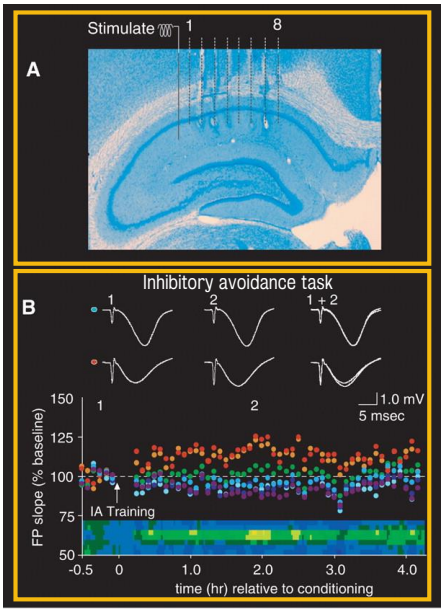
Researchers have asked the following question:
Can training in a hippocampus dependent memory task induce LTP?



Passive avoidance task

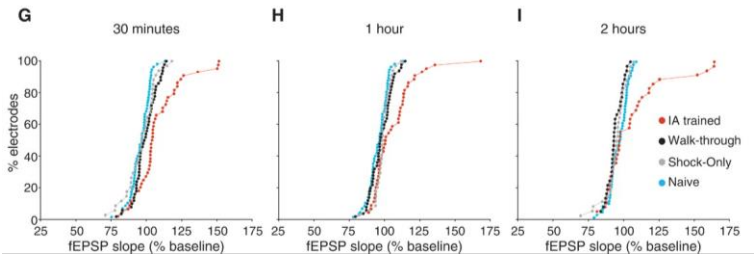


Occurrence of LTP (1)



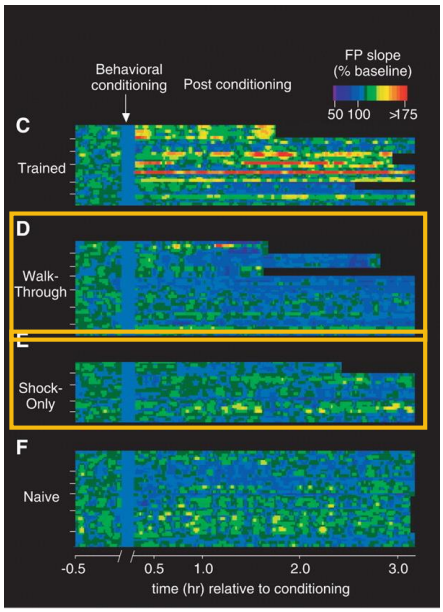
Behaviour is used to induce LTP:

Only a small set of synapses undergo LTP, hence the need for multiple electrodes to detect it.



Whitlock et al. (2006)

Occurrence of LTP (2)



No LTP was induced in the **performance controls**.

LTP was induced only in animals trained in the inhibitory avoidance task, showing **that behavioural training can induce LTP.**

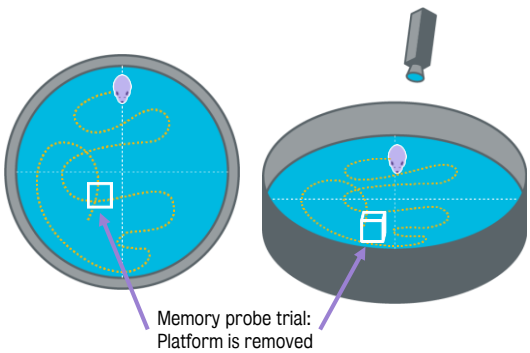
Whitlock et al. (2006)
Learning induces long-term potentiation in the hippocampus

LTP occurs during **memory formation**.

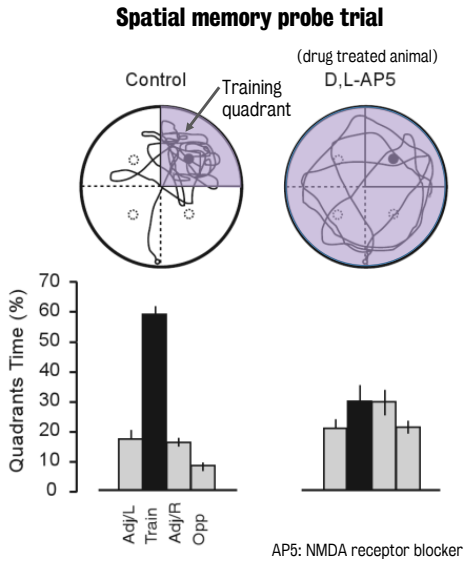
Whitlock et al. (2006)

Block of LTP correlates with impaired memory formation

The following experiments tested the impact of LTP manipulation on the water maze behaviour task.



Block of LTP and spatial memory



AP5: NMDA receptor blocker

This study shows:

- drug treated animals have a random surge, indicating that they have no spatial memory
- control animals show spatial memory awareness
- blocking the NMDA receptor impairs spatial learning

Important to note:

- the drug dose in these experiments was relatively high, resulting in performance abnormalities amongst some of the animals
- blocking NMDA receptors not only blocks the induction of LTP but also blocks long term depression

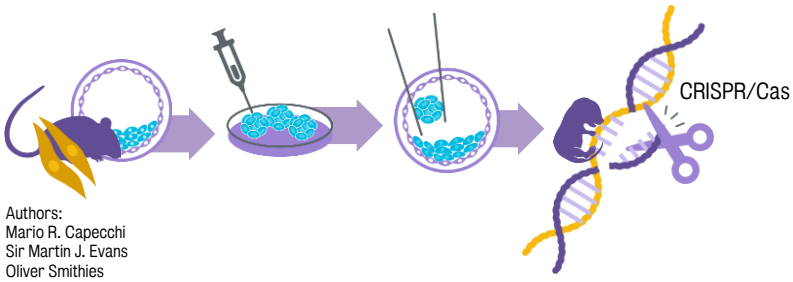
Morris et al. (1986)

General strategy for gene targeting in mice

LTP can be blocked by generating mutant mice.

Whilst a limited number of drugs allow us to block particular molecules, genetics allow us to manipulate any gene of interest.

In 2007, the Nobel Prize committee awarded the **Nobel Prize for gene targeting in manipulating the mouse genome**.



Authors:
Mario R. Capecchi
Sir Martin J. Evans
Oliver Smithies

Rationale:

Impairment of the molecular process

Impairment of LTP

Impairment of learning and memory

The Nobel Prize in Physiology or Medicine 2007 (2019)

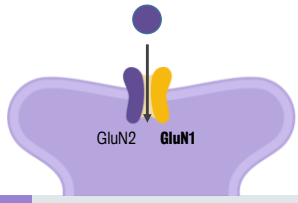
Region-restricted knockout mice

Susumu Tonegawa
Nobel laureate

Received the Nobel prize for his **discovery of antibody diversity.**

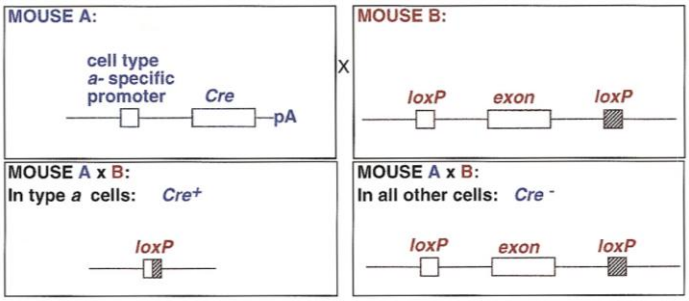
Method of study:
Knock out an essential NMDA receptor subunit (GluN1) exclusively in the hippocampus and study its impact.

Result:
Tonegawa succeeded in having a mutant mouse with an active Cre recombinase exclusively in the CA1 hippocampal area



Knocking out the gene that encodes GluN1 blocks NMDA receptors

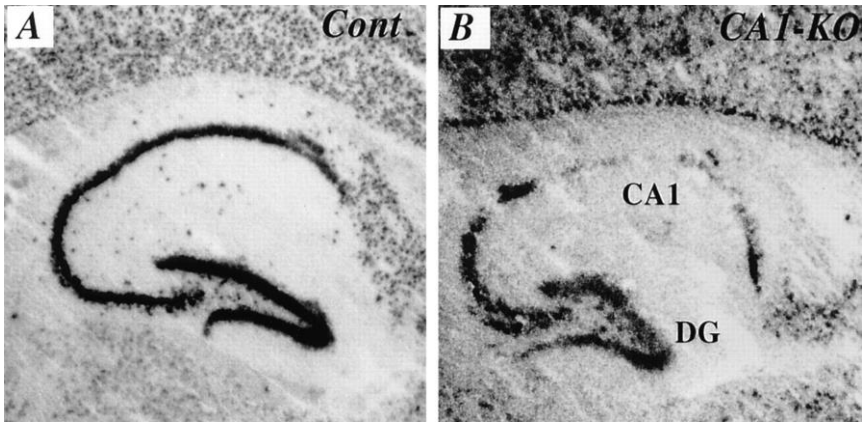
Conditional knock out



Tsien et al. (1996)

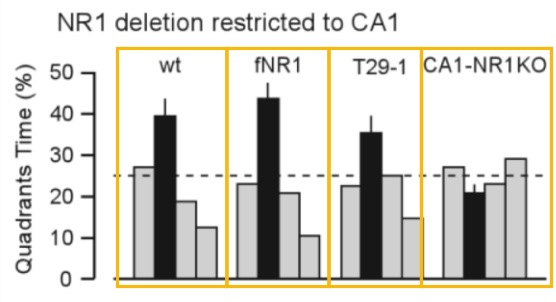
Region-restricted KOs

Result:
There was a lack of the NMDA subunit in the CA1 region



Tsien et al. (1996)

Block of LTP and spatial memory



Knocking out NMDA receptors in the CA1 area impairs spatial learning.

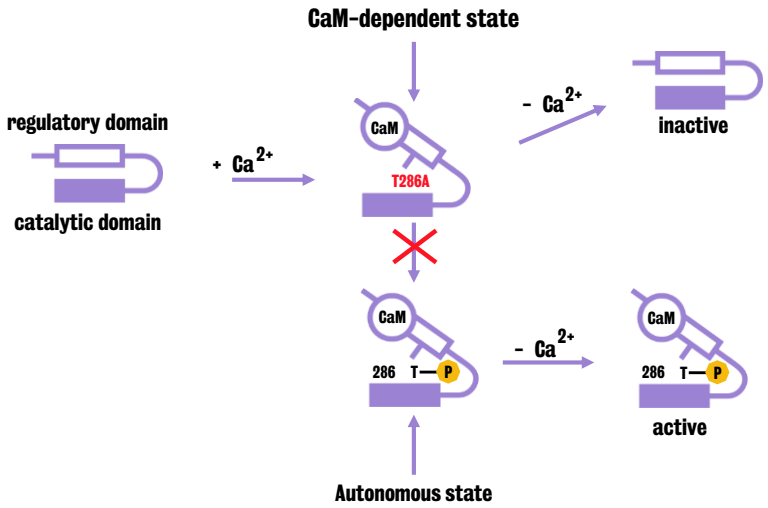
The findings from this study are consistent with the ones where the pharmacological blockage of the NMDA receptors results in the blockage of spatial memory.

However, NMDA receptors can also block long-term depression.

αCaMKII-T286A mutants

CaM Kinase II:

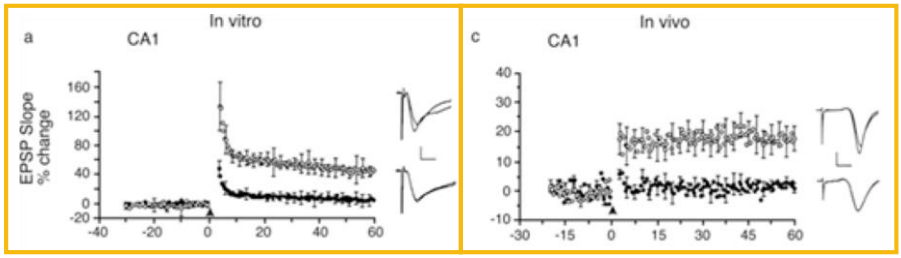
a calcium calmodulin-dependent kinase.



Genetic block of LTP in hippocampus

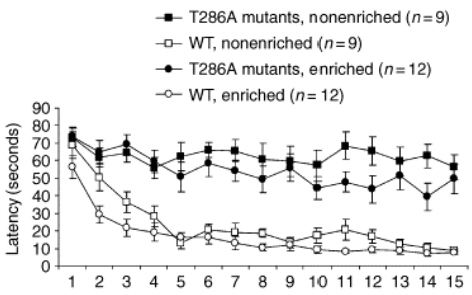
These animals have severely impaired LTP in CA1 in the hippocampus.

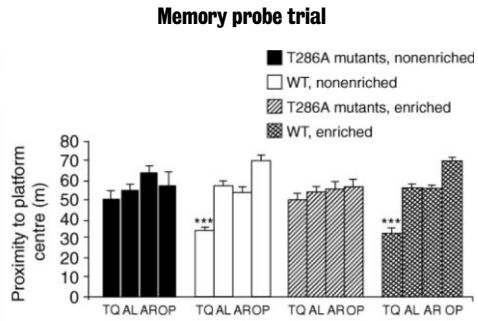
Finding:
Autophosphorylation of CaMKII at threonine-286 is fundamentally important for the induction of LTP.



Cooke et al. (2006)

Impaired spatial learning and memory in T286A mutants



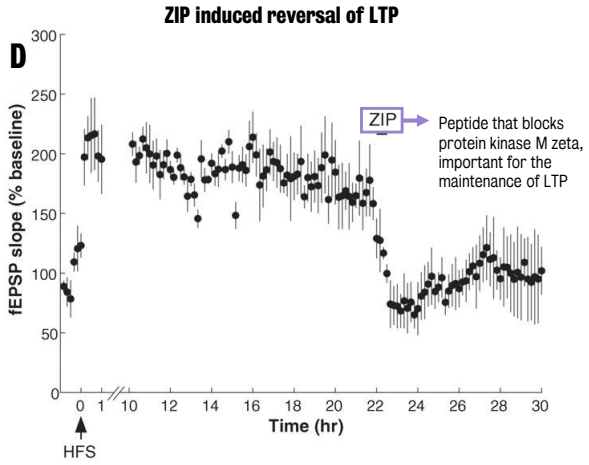


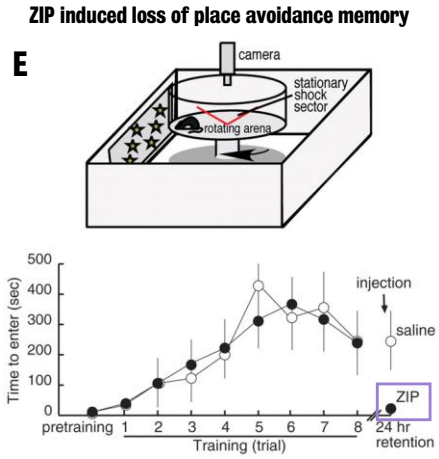
Finding:

- wild-type animals have a selective surge in the target quadrant, while various mutants have a random surge, indicating no spatial memory in the latter
- mutants lack LTP induction and spatial memory, further strengthening the correlation between LTP and memory

Need and Giese (2003)

Block of LTP maintenance impairs established memory





Finding:

- ZIP erased the memory in these animals and consequently also erased LTP. This shows the existence of a strong correlation between LTP and memory maintenance.

Pastalkova et al. (2006)

Lecture summary

There is very strong evidence that **LTP is a memory mechanism**.

It follows Hebb's postulate.

We have seen that:

- LTP can be induced by behavioural training
- blocking LTP induction seems to block spatial memory formation
- blocking LTP maintenance seems to erase spatial memory

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Attributions

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End of topic