LEARNING & MEMORY
LONG-TERM POTENTIATION
SKKU GBME GRAD CLASS
KIM HF
The long-term potential of LTP

Robert C. Malenka

Figure 1 | Number of long-term potentiation (LTP) publications since 1976.
Memory and Synaptic Plasticity

Memories are stored as alterations in the strength of synaptic connections between neurons in the CNS.

What is the Synaptic plasticity?

In neuroscience, synaptic plasticity is the ability of synapses to strengthen or weaken over time, in response to increases or decreases in their activity. Plastic change also results from the alteration of the number of neurotransmitter receptors located on a synapse.

- The capacity for alterations of synaptic connections between neurons.
Hebb’s Postulate

When an axon of cell A is near enough to excite cell B or repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased.

What is the Hebb synapse?

Hebb synapses are modifiable synaptic connections that increase their efficacy when the presynaptic and postsynaptic neurons are coactive.
Memory and Synaptic Plasticity

Memories are stored as alterations in the strength of synaptic connections between neurons in the CNS.

Synaptic plasticity
- The capacity for alterations of synaptic connections between neurons.

Long-Term Potentiation (LTP)
- The specific form of synaptic plasticity.
- The leading candidate as a mechanism subserving behavior-modifying changes in synaptic strength that mediate learning and memory in mammals.
Synaptic Plasticity and LTP

Bliss and Lomo’s first published LTP experiment.
Perforant path.
Recording synaptic responses in the dentate gyrus
Stimulating the entorhinal cortex
What are the three pathways in hippocampus?

- Schaffer collaterals
- Mossy fibers
- Perforant pathway
Bliss and Lomo’s first published LTP experiment.

Perforant path.
Recording synaptic responses in the dentate gyrus
Stimulating the entorhinal cortex
Extracellular stimulating and recording.
Tetanic stimulation (100Hz, 1 second) → LTP
Various types of LTPs

- Mossy fibers
- Perforant pathway
- Schaffer collaterals
Synaptic Plasticity and LTP

Which pathway did the researcher stimulate?
How many LTP can you test in principle?
Recording Configuration and Typical Physiologic Responses

Stimulating Schaffer Collaterals in Area CA3

Recording in Stratum Pyramidale in Area CA1

Recording in Stratum Radiatum in Area CA1

Stimulus Artifact

An indication of the pre-synaptic action potential arriving at the recording site

Excitatory post-synaptic potential, Synaptic activation in the CA1 pyramidal neurons
Recording Configuration and Typical Physiologic Responses

The initial slope of EPSP or Absolute peak amplitude

The initial slope is less subject to contamination from noises
Baseline Synaptic Transmission

Test stimulus intensity

: $\sim 30\text{-}50\%$ of the maximum response recorded during the I-O measurements.
LTP
WHAT’S THE SHORT-TERM PLASTICITY?
Short-Term Plasticity: PPF and PTP

Paired-pulse facilitation (PPF)

Post-tetanic potentiation (PTP)
One second 100 Hz stimulation (or three trains separated by 20 seconds or more)
MOLECULAR MECHANISMS

NMDA receptor
The N-methyl-D-aspartate receptor (also known as the NMDA receptor or NMDAR), is a glutamate receptor and ion channel protein found in nerve cells. It is activated when glutamate and glycine (or D-serine) bind to it, and when activated it allows positively charged ions to flow through the cell membrane.

What's the most important in the structure for synaptic plasticity? & Why?
How can you test the effect of NMDAR in LTP?
NMDA receptor antagonist APV blocks the induction of LTP.
NMDA Receptor-Dependence of LTP

LTP induced by Theta-Frequency Stimulation (TFS)

30 seconds of single stimuli delivered at 5Hz

NMDA receptor dependent

Is there any reason why the TFS was used?
NMDA Receptor-Dependence of LTP

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Is there any reason why the TFS was used?

The "hippocampal theta rhythm" is a strong oscillation that can be observed in the hippocampus and other brain structures in numerous species of mammals including rodents, rabbits, dogs, cats, bats, and marsupials.

Hippocampal theta waves, with a frequency range of 4–7 Hz (human)
NMDA Receptor-Dependence of LTP

1. LTP induced by Theta-Burst Stimulation (TBS)

- 5-Hz burst frequency
- 10 Hz bursts per train
- 3 trains, 20-sec intertrain interval

NMDA receptor dependent

A

B

fEPSP slope (% of baseline)

Time (min)
NMDA Receptor-Dependence of LTP

2. Pairing Long-Term Potentiation

The paired input
- stimulated at 2 Hz 40 times

CA1 pyramidal neuron
- depolarized from -70 mv to 0 mV

The control input
- no stimulation
A glutamate gated channel
A voltage-dependent channel
Calcium channel

open

Elevated intracellular calcium in the post-synaptic neuron

Various calcium-dependent processes

LTP induction

How is this depol. possible in vivo?
Synaptically Controlled Associated Signals
Back Propagating Action Potentials

Back propagation

dendrite

cell body
Synaptically Controlled Associated Signals

The role of back propagating dendritic action potentials in the induction of LTP

When does the LTP or LTD occur?

NMDA receptor dependent
NMDA Receptor-Independent LTP

Insensitive to NMDA receptor selective antagonist such as APV

Blocked by blockers of voltage-sensitive calcium channels

Current model:

- 200 Hz stimulation elicits **sufficiently large and prolonged membrane depolarization**, resulting in the opening of voltage-dependent calcium channels, to trigger elevation of post-synaptic calcium sufficient to trigger LTP.
NMDA Receptor-Independent LTP

Tetra-Ethyl Ammonium (TEA) LTP

TEA: a non-specific potassium channel blocker
   Increases membrane excitability

Insensitive to NMDA receptor antagonists

Blocked by blockade of voltage-sensitive calcium channels

Current model

: Synaptic depolarization due to K+ channel blockade leads to the triggering of LTP through post-synaptic calcium influx.
NMDA Receptor-Independent LTP

Mossy Fiber LTP

Pre-synaptic specialization
A Role for Calcium Influx in LTP

Injection of calcium chelators post-synaptically blocks the induction of LTP. Inhibitors of a variety of calcium-activated enzymes block LTP induction.

→ Block

Fluorescent imaging experiments using calcium-sensitive indicators: post-synaptic calcium is elevated with LTP-inducing stimulation.

→ Measure

Elevating post-synaptic calcium is sufficient to cause synaptic potentiation.

→ Mimic
Pre- versus Post-Synaptic Mechanisms

Increase of EPSP

Pre-synaptic mechanism: Increase in neurotransmitter release
or
Post-synaptic mechanism: Change in glutamate receptor responsiveness
Pre- versus Post-Synaptic Mechanisms

Presynaptic = Altered
• Neurotransmitter amount in vesicles
• Number of vesicles released
• Kinetics of release
• Glutamate reuptake
• Probability of vesicle fusion

Postsynaptic = Altered
• Number of AMPA receptors
• Insertion of AMPA receptors
• Ion flow through AMPA channels
• Membrane electrical properties

Additional possibilities include changes in number of total synaptic connections between two cells.
Silent Synapses

- NMDA Receptor
- AMPA Receptor
- Vesicle

Silent Synapse

Depolarization

Back propagating Action Potential
Retrograde signaling

Physical Coupling (i.e. Integrins)

Diffusible Messengers (i.e. NO, O$_2^-$, AA)
Pre- versus Post-Synaptic Mechanisms

Changes occur in both the pre-synaptic and post-synaptic compartments.

**Presynaptic** = Altered
- Neurotransmitter amount in vesicles
- Number of vesicles released
- Kinetics of release
- Glutamate reuptake
- Probability of vesicle fusion

**Postsynaptic** = Altered
- Number of AMPA receptors
- Insertion of AMPA receptors
- Ion flow through AMPA channels
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Additional possibilities include changes in number of total synaptic connections between two cells.
LTP induction & expression
COMPONENTS OF LTP
Stimulating Schaffer Collaterals in Area CA3

Recording in Stratum Pyramidale in Area CA1

Population spike

Recording in Stratum Radiatum in Area CA1

Increased Action Potential Component of LTP

Pre-tetanus

Post-tetanus

2.00 mV

4 ms
Two Components of LTP

1. Increased EPSP

2. Increased Action Potential Firing
EPSP-spike (E-S) Potentiation

What is the mechanism for this long-term increase in the likelihood of firing an action potential?

→ Changes in post-synaptic neuron

Long-term down-regulation of dendritic potassium channel function

↓

Persistent increase in cellular excitability

↓

Increase of action potential firing
What is the mechanism for this long-term increase in the likelihood of firing an action potential?

GABAergic interneurons in area CA1

Use the inhibitory neurotransmitter GABA
Inhibit firing of CA1 pyramidal neurons

Diminished Cl⁻ channel function produces increased excitability

EPSP-spike (E-S) Potentiation
Three mechanisms of LTP

Induction

The transient events serving to trigger the formation of LTP

Maintenance & Expression

LTP is maintained by the persisting biochemical signal that lasts in the cell, and this persisting biochemical signal acts on an effector (e.g. AMPA receptor), resulting in the expression of LTP.
Three mechanisms of LTP

- **INDUCTION BLOCKED**
- **EXPRESSION BLOCKED**
- **MAINTENANCE BLOCKED**

- PERIOD OF DRUG TREATMENT
- LTP EXPRESSION BLOCKED
- MAINTENANCE BLOCKED
- INDUCTION BLOCKED
Three phases of LTP

Immediate LTP (I-LTP)
- The first stage of LTP
- Lasts about 30 min

Early LTP (E-LTP)
- Subserved by persistently activated protein kinases
- Starts at 30 min and is over by about 2-3 hours.

Late LTP (L-LTP)
- Dependent on changes of gene expression
- Many hours or more
Three phases of LTP

Induction → I-LTP maintenance → Expression

Induction → E-LTP maintenance → Expression

Induction → L-LTP maintenance → Expression
Modulation of LTP Induction

Stimulating Electrode

Recording Electrode

Denervated preparation

Loss of modulatory inputs

Partial reconstitution:
Applying the neurotransmitter to the slice preparation

Modulatory inputs of the neurotransmitters dopamine (DA), norepinephrine (NE), serotonin (5HT), and acetylcholine (Ach) in the intact animal.
Modulation of LTP Induction

Iso: Isoproterenol
Beta-adrenergic agonist

Carbachol: Acetylcholine receptor agonist
6-CI-PB: dopamine receptor agonist

Modulation of back-propagating AP
**Saturating LTP blocks Memory Formation**

What’s the logic in these experiments?

LTP stimulation before learning

![Diagram showing the effects of LTP stimulation on memory formation.](image-url)
Depotentiation and Long-Term Depression

A synapse involved in permanent memory storage

- Immutable change in synaptic strength

A synapse in the area that are not sites of permanent memory storage, but whose plasticity is part of the active processing in forming new long-term memories.

- The potentiation must be reversible.

Depotentiation: activity-dependent reversal of LTP

Long-term depression (LTD): long-lasting decrease of synaptic strength below baseline
Depotentiation and Long-Term Depression

Long-Term Depression

Depotentiation
Involvement of LTP in spatial learning and memory consolidation?

LTP ≠ Memory

One of essential processes contributing to memory formation
LTP and Hippocampal-dependent Memory

Pre-training infusion
DL-APV: active form
L-APV: inactive form

Control  DL-AP5  L-AP5

Pre-training infusion
DL-APV: active form
L-APV: inactive form

Control  DL-AP5  L-AP5

Pre-training infusion
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Pre-training infusion
DL-APV: active form
L-APV: inactive form

Control  DL-AP5  L-AP5

Pre-training infusion
DL-APV: active form
L-APV: inactive form

Control  DL-AP5  L-AP5
AP5 affect the induction of LTP.
LTP in multimodal information processing

**A: Example 1**

- **At start:**
  - $1$ can fire AP
  - or $2$ together with $3$, $3$ can fire AP

- **Paired activity:**
  - $1 + 2 \rightarrow \text{LTP @ 2}$
  - $1 + 3 \rightarrow \text{LTP @ 3}$

- **Input 1 (strong)**
- **Input 2 (Ach)**
- **Input 3 (weak)**

- **Input 1 fires AP**
- **Input 2 gates bpAP into distal dendrites**
- **Input 3 potentiated**

- **Now input 3 sufficient to trigger AP and give a readout equivalent to input 1**

**B: Example 2**

- **Input 1 (strong)**
- **Input 2 (Ach)**
- **Input 3 (potentiated)**

- **2 alone and 3 alone can now fire an AP.**
- **Therefore now 2 alone or 3 alone can reconstitute 1 or 2 + 3**
Timing-dependent Information Storage in the Hippocampus

Trace fear conditioning

CS \[\rightarrow\] US

Time

Delayed match-to-place task

Cue \[\rightarrow\] Delay \[\rightarrow\] Response

(Sample) \[\rightarrow\] (Test)

NMDA receptor activation is necessary for both.

\[\Rightarrow\] LTP is involved in timing-dependent information storage.
LTP and Memory Consolidation

Blocking LTP-related molecular processes in the hippocampus
(e.g. infusion of NMDA receptor blocker)

⇒ Disruption of memory consolidation

LTP is participating in the consolidation of hippocampus-dependent memory formation.
PAPERS

What is the LTP?

Synaptic plasticity, memory and the hippocampus: a neural network approach to causality

Guilherme Neves, Sam F. Cooke* and Tim V. P. Bliss

What is the reconsolidation?

Synaptic Protein Degradation Underlies Destabilization of Retrieved Fear Memory

Sue-Hyun Lee, Jun-Hyeok Choi, Nuribalhae Lee, Hye-Ryeon Lee, Jae-Ick Kim, Nam-Kyung Yu, Sun-Lim Choi, Seung-Hee Lee, Hyoung Kim, Bong-Kiun Kaang*

Neuroscience Update

Synaptic Protein Degradation as a Mechanism in Memory Reorganization

Bong-Kiun Kaang, Sue-Hyun Lee, and Hyoung Kim


A Million Dollar Question: Does LTP = Memory?

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NEXT CLASS…

Operant conditioning