Pre-Lecture Video

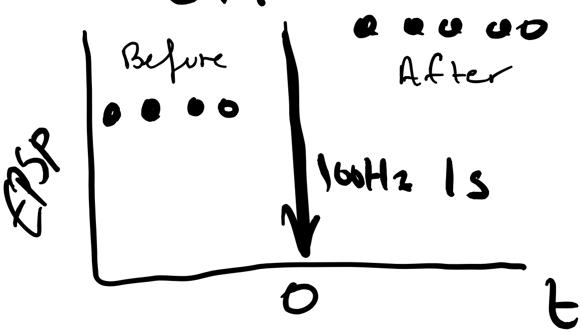
LTD: Synaptic connection b/t neurons __weakens__

- resets previous synaptic changes → new memories can be formed

LTD occurs after slow low intensity stimulation.

LTP: Synaptic connection b/t neuron **strengthens**

LTP

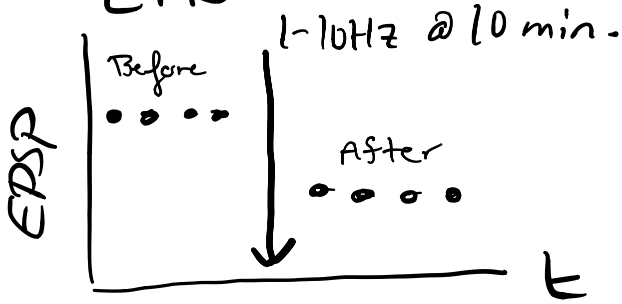


$[Ca^{2+}]_R = 100nM$

$[Ca^{2+}]_{HFS} = 1\mu M$

CAMKII →

LTD



$[Ca^{2+}]_R = 100nM$

$[Ca^{2+}]_{LFS} = 400nM$

Calcineurin →

Lecture 17. Learning 2- Long Term Potentiation and Depression

Professor Christiane Linster

Pre-lecture preparation

(1) Watch pre-lecture video on long term potentiation and long term depression
(2) Read pages 815 – 818; Figures 23.28, 23.29, 23.30
(3) Read pages 874 – 885; Figures 25.5, 25.6, 25.7, 25.8, 25.9, 25.11, 25.13, 25.14, 25.15

Learning Objectives

To understand the nature of long term potentiation (LTP) and long term depression (LTD)
(1) Be able to understand classical LTP/LTD experiments
(2) Be able to relate LTP/LTD to NMDA receptor function
(3) Be able to relate the induction of LTP to the idea of an "AND" gate
(4) Be able to apply concepts of LTP and LTD to a simple learning circuit
(5) Understand how LTP/LTD function is modulated by neuronal state

Lecture Outline

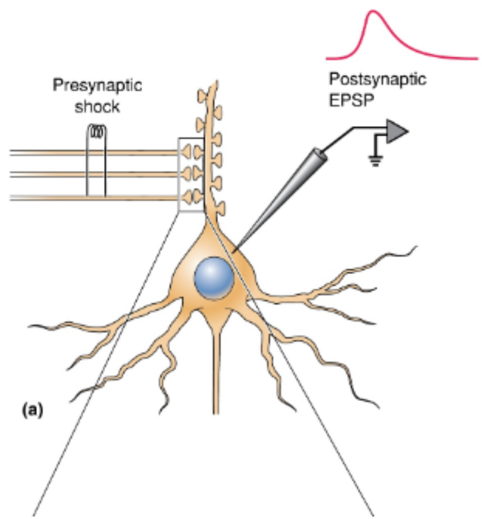
(1) Learning induces changes in neural communication; two of these types of changes has been termed LTP and LTD. Experimentally, LTP/LTD can be induced by stimulating presynaptic fibers as well as a postsynaptic neuron to be active (depolarized) at the same time. Depending on the degree of activity, synaptic strength or efficacy will increase or decrease (Figures 23.28-30 and associated text). Classically, activity in the presynaptic neuron is measured in terms of action potentials (number, frequency) and activity in the postsynaptic neuron is measured as degree of depolarization (positive voltage change with respect to rest). The exact combination of "activity" which leads tp LTP or LTD is synapse and neuron specific and needs to be determined experimentally for each neural circuit specifically.
(2) This type of plasticity lends itself to associate events/contexts/stimuli together. We will illustrate this idea on a simple example of behavioral and neural plasticity (Figure 25.17 page 887)
(3) Several molecular processes are involved in the induction, expression and maintenance of plasticity and can be related to temporal aspects of memory processes (Figures 25.5 – 15 and associated text).
(4) Plasticity and learning can be modulated by the 'state' of the animal (stress, attention, hunger ..) as well as the 'state' of the cells involved (ion concentrations, depolarization, excitability ..)

Study Questions

1) Why can LTP be induced using either a fast stimulation of only presynaptic fibers OR a slow stimulation of presynaptic fibers accompanied by depolzairxation of the postsynaptic cell?
2) Would a neuromodulator that depolarizes cells speed up or slow down LTP type plasticity?
3) Given what you know about the role of Ca+ in induction of LTP and LTP, if fast and slow spiking were induced in cells, would both occur or only one?
4) How could LTP change with a very Mg+ depleted diet? If you look at advertisements for Mg+ supplements do they make sense to you?

Lecture 17: Learning at the synaptic level: LTP and LTD

Christiane Linster
CL243@cornell.edu
W247 Mudd Hall
Office hours Wed. 1:30-2:30 or by appointment



Lectures 16-21: Learning and memory

Lecture 16 NMDA receptor allows to “associate” two events at the level of a synapse

Lecture 17 **Learning at the synaptic level: LTP and LTD**

Lecture 18 Learning at the network level: how are LTP and LTD involved in changing networks ?

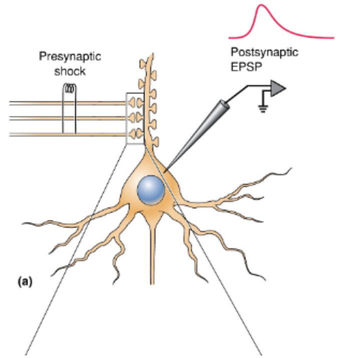
Lecture 19 Learning while behaving: sequences of events and STDP

Lecture 20 Remembering: Consolidation of what has been learned

Lecture 21 What is a memory?

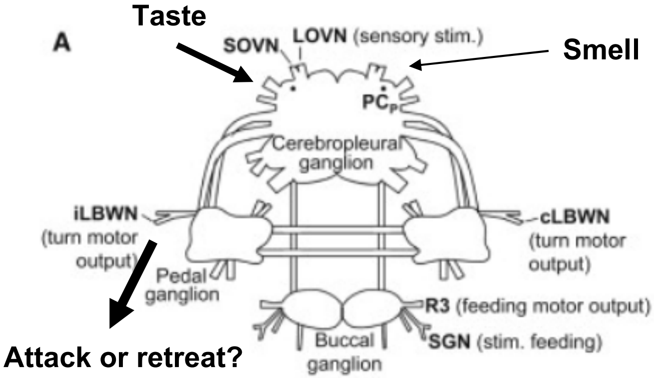
Lecture 17: Learning 1

Learning at the synaptic level: LTP and LTD

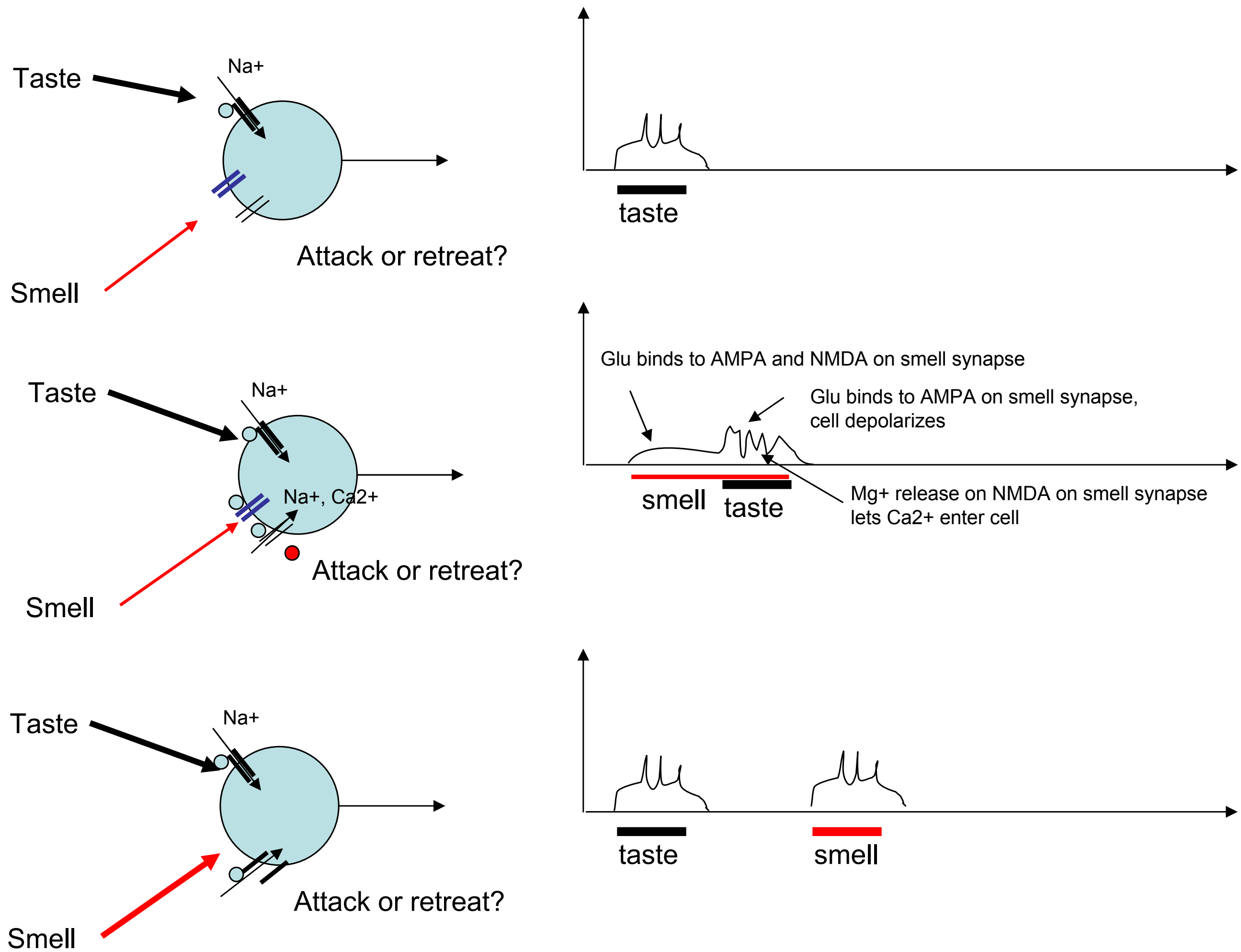


(1) Be able to understand classical LTP/LTD experiments
(2) Be able to relate LTP/LTD to NMDA receptor function
(3) Be able to relate the induction of LTP to the idea of an “AND” gate
(4) Be able to apply concepts of LTP and LTD to a simple learning circuit
(5) Understand how LTP/LTD function is modulated by neuronal state

Review

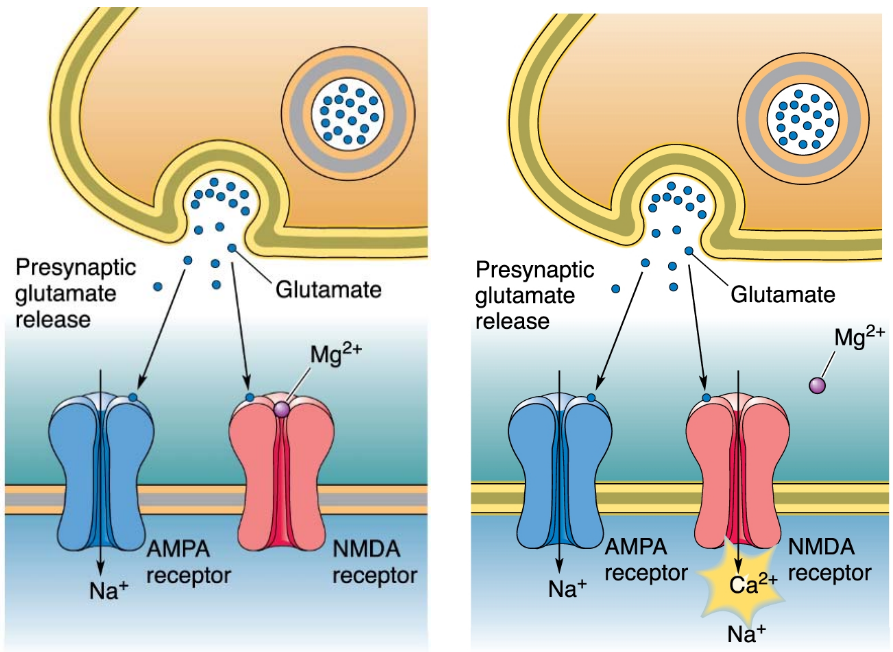


A Neuronal Network Switch for Approach/Avoidance Toggled by Appetitive State. Current Biology, 2011; DOI: 10.1016/j.cub.2011.10.055 http://www.cell.com/current-biology/r...



Taste
Na+
Smell
Attack or retreat?
taste
Taste
Na+
Na+, Ca2+
Smell
Attack or retreat?
Glu binds to AMPA and NMDA on smell synapse
Glu binds to AMPA on smell synapse,
cell depolarizes
smell
taste
Mg+ release on NMDA on smell synapse
lets Ca2+ enter cell
Taste
Na+
Smell
Attack or retreat?
taste
smell

NMDA receptors detect simultaneous pre- and postsynaptic activity



(a) Postsynaptic membrane at **resting** potential

(b) Postsynaptic membrane at **depolarized** potential

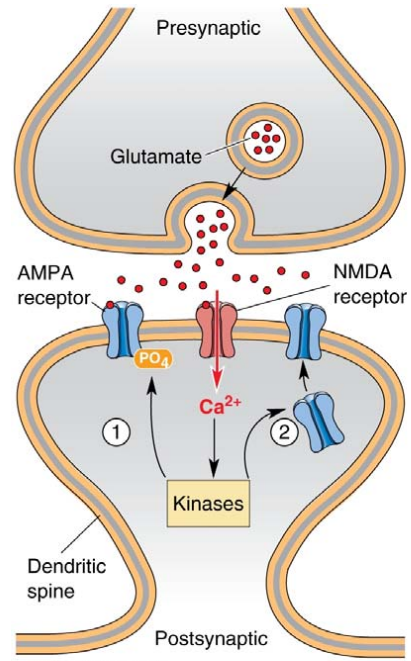


Figure 23.28 textbook

Experimental induction of plasticity

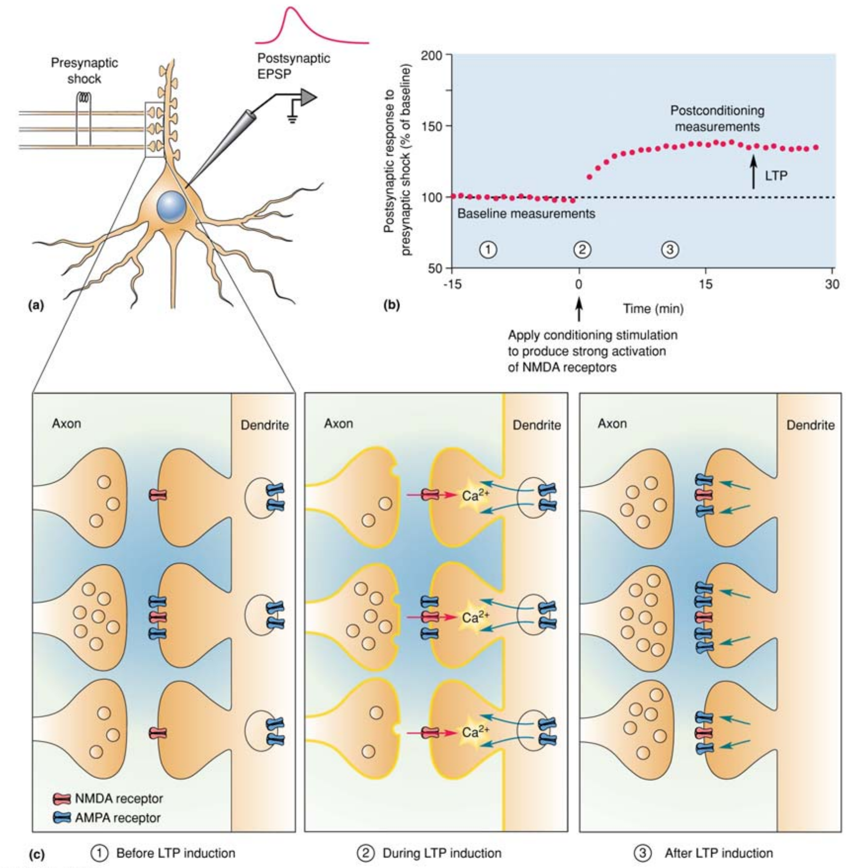
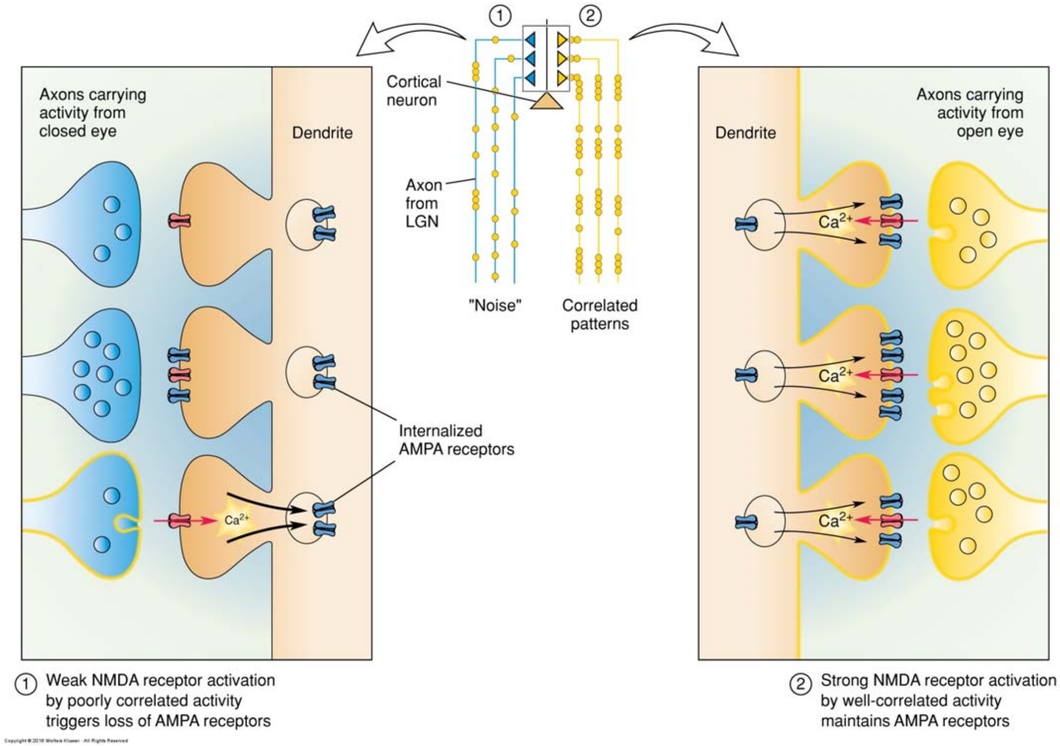


Figure 23.29 textbook

Experimental induction of plasticity



Developmental and adult plasticity use many of same mechanisms!

Figure 23.30 textbook

Experimental induction of plasticity

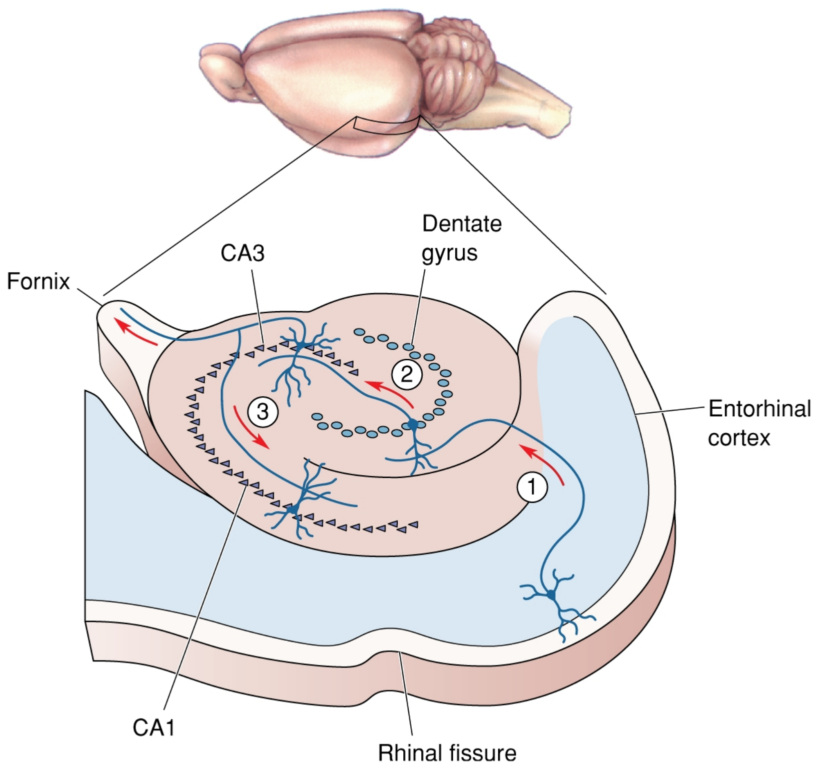


Figure 25.5 textbook

Experimental induction of plasticity

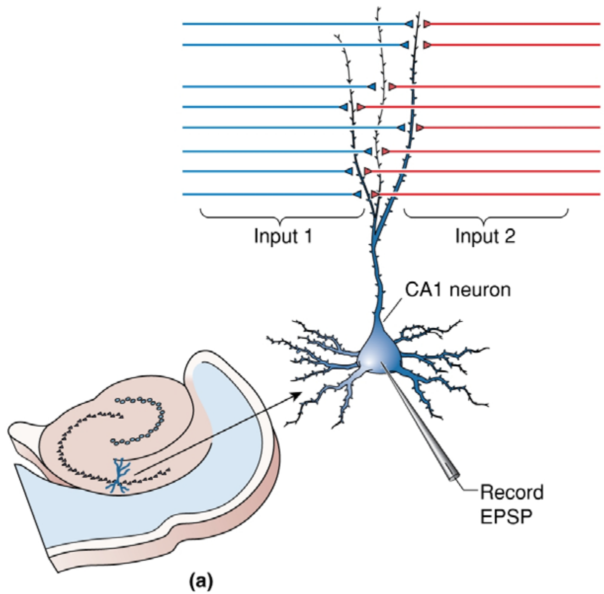
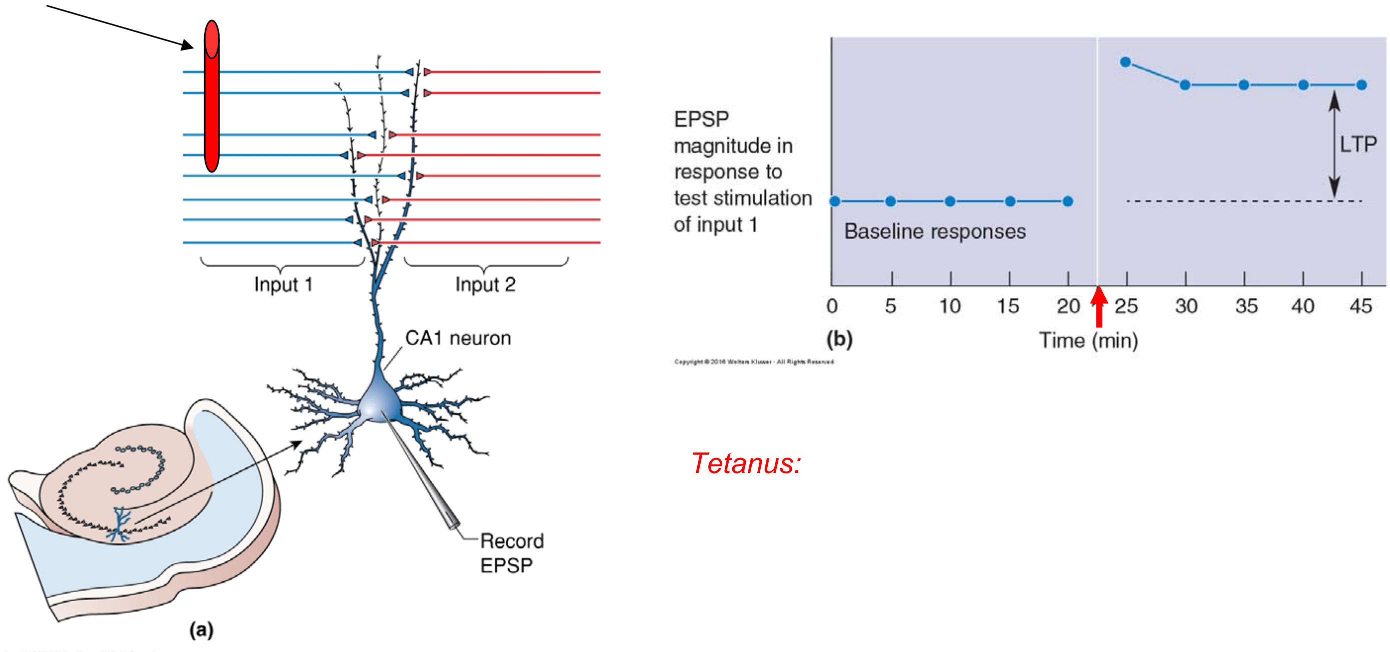


Figure 25.6 textbook

Experimental induction of plasticity

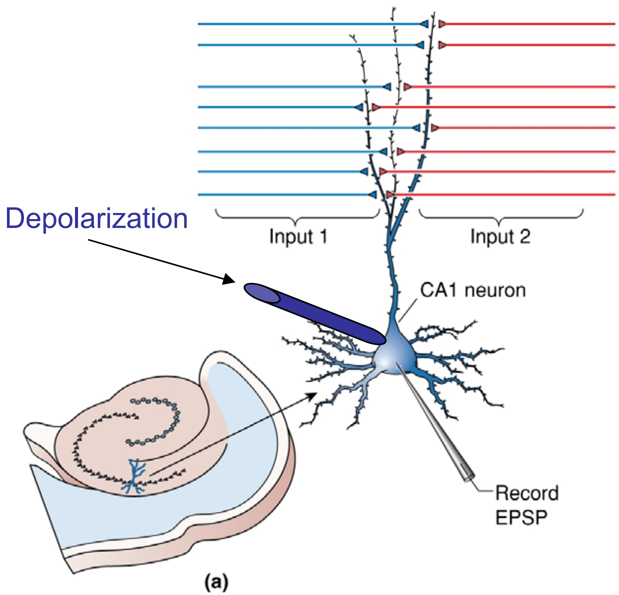
Electric stimulation

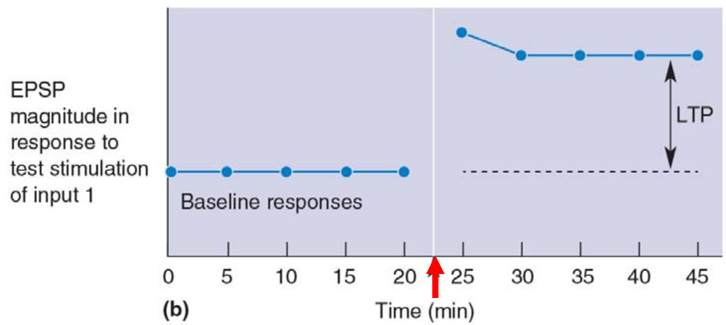


Tetanus:

Figure 25.6 textbook

Experimental induction of plasticity





Tetanus:

or

Depolarization

Figure 25.6 textbook

How do tetanus and depolarization compare?

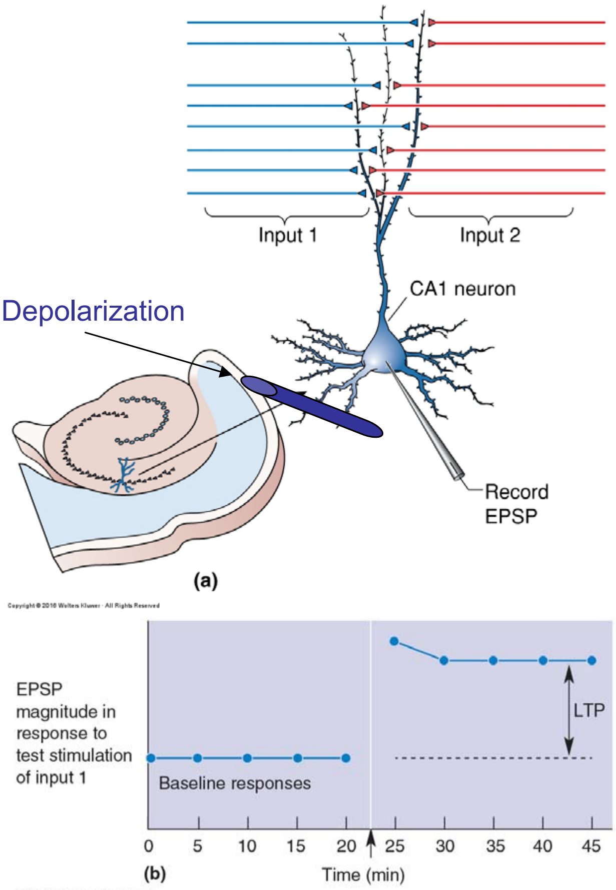
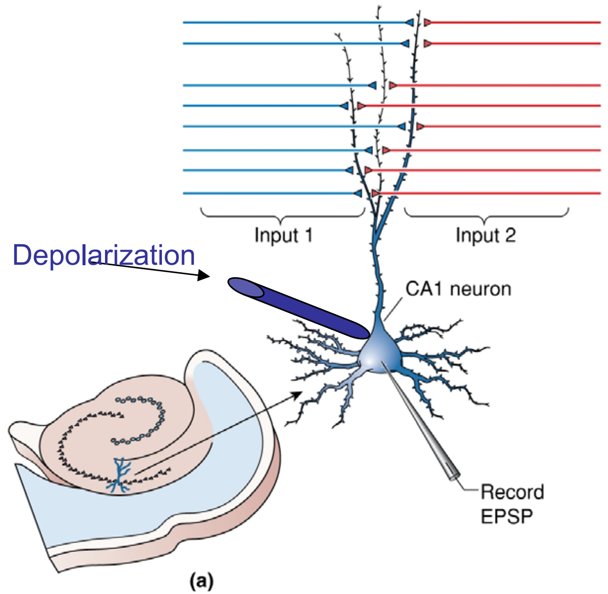
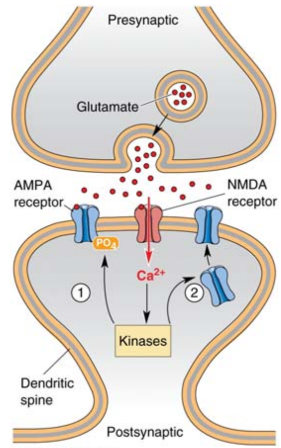


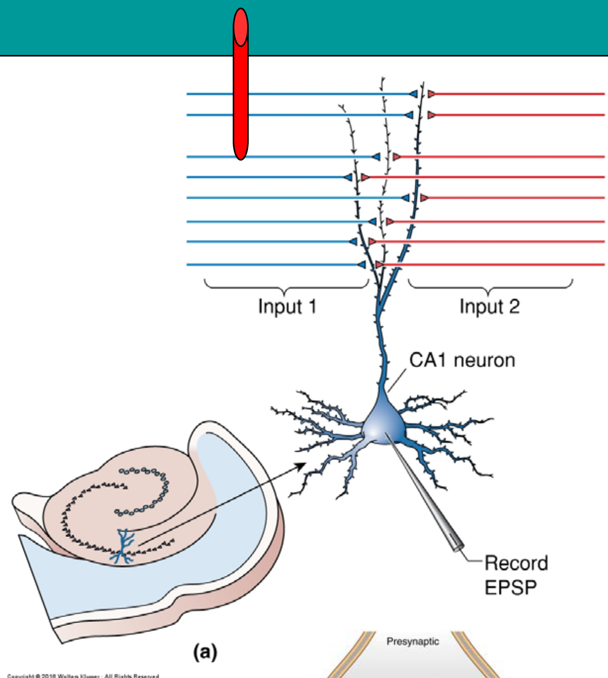
Figure 25.6 textbook

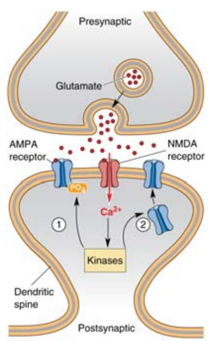
How do tetanus and depolarization compare?



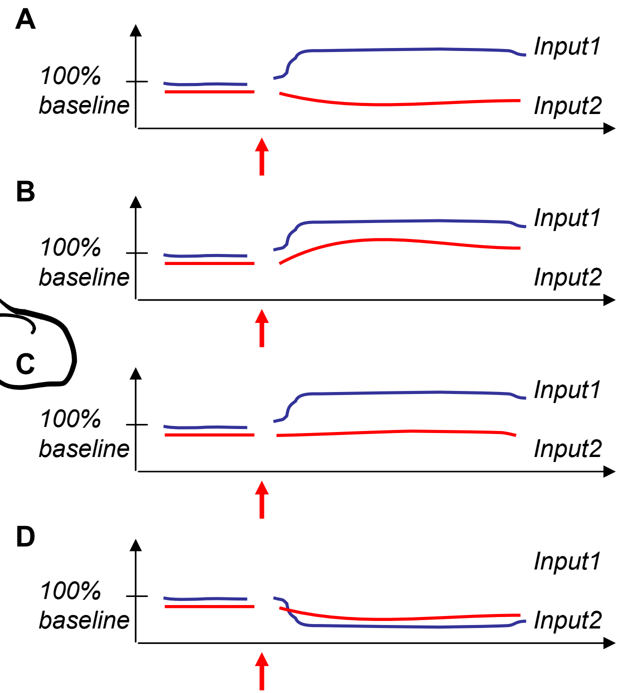


Clicker question

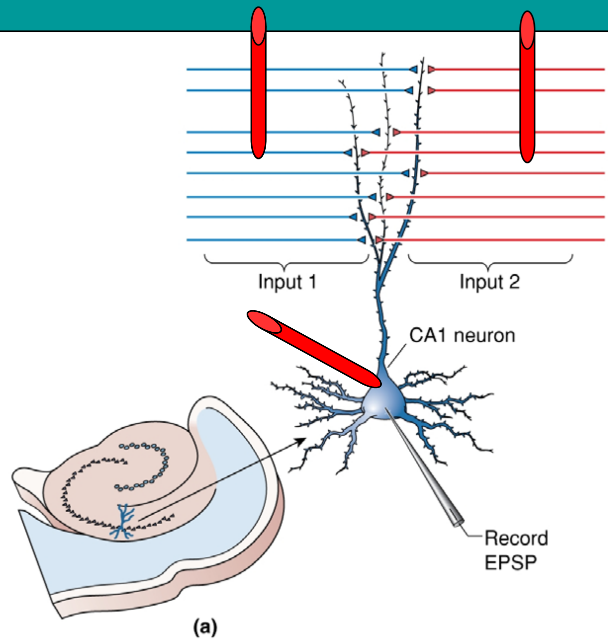




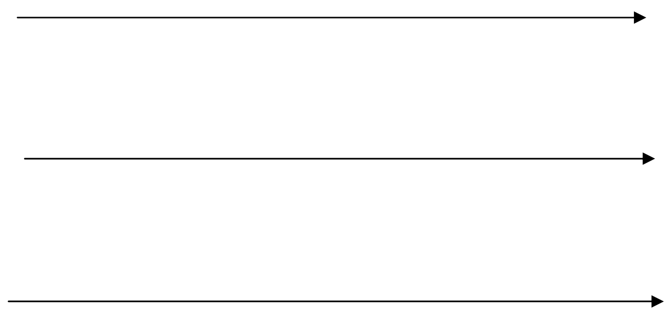
If you give a tetanus stimulation to Input1 only, what do you expect the EPSP recordings for each input to look like?



Clicker question

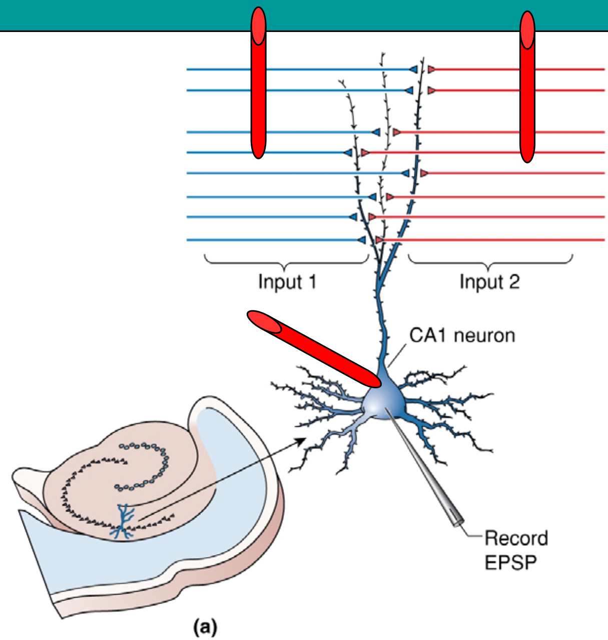


If you depolarize the postsynaptic cell while alternately stimulating Inputs 1 and 2, what do you expect the EPSPs to look like after?

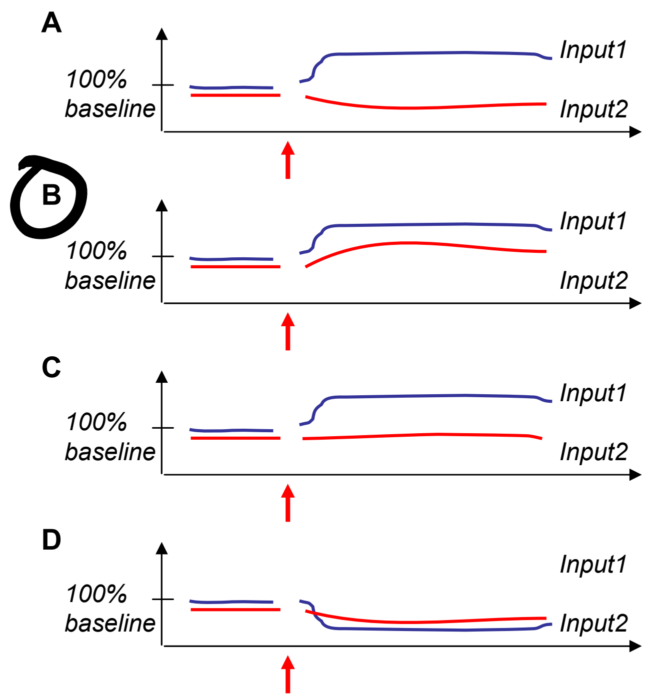


RAMI Pellumbi

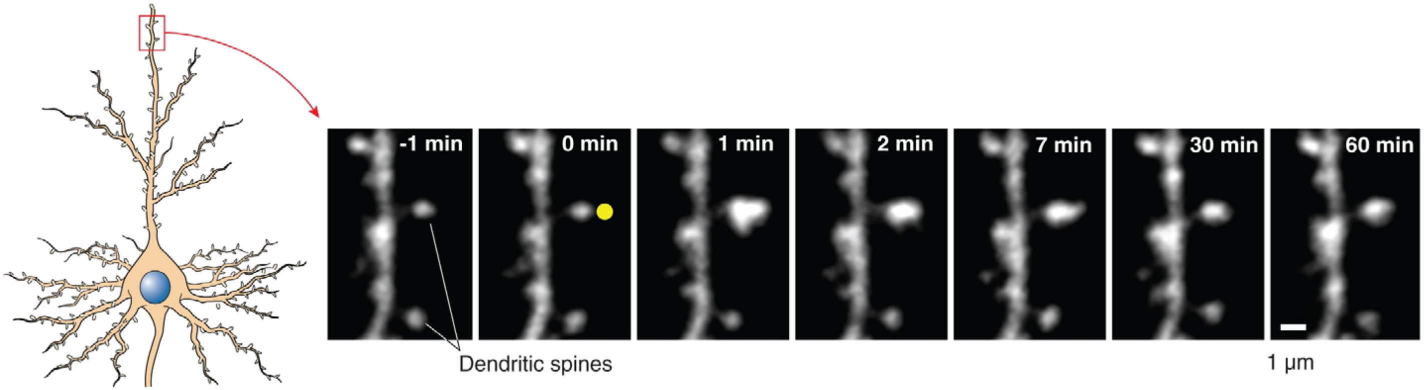
Clicker question

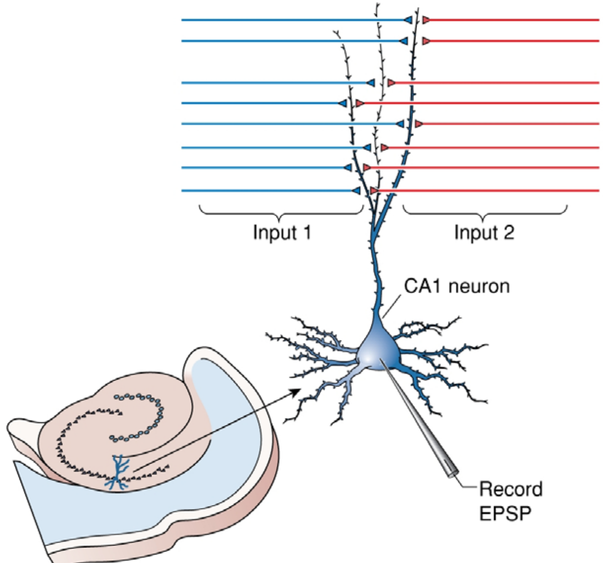


If you depolarize the postsynaptic cell while alternately stimulating Inputs 1 and 2, what do you expect the EPSPs to look like after?

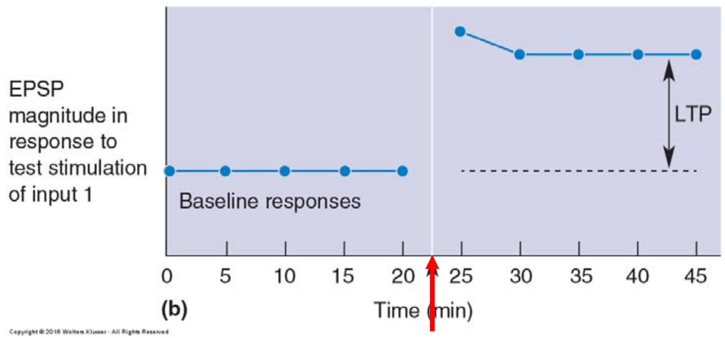


Synapses can grow under plasticity promoting conditions



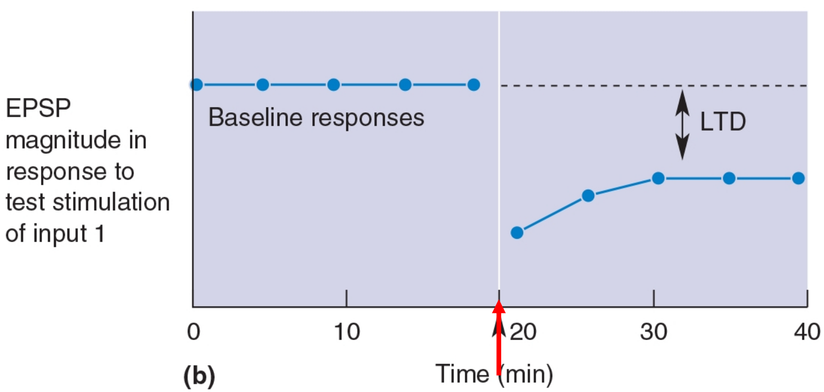


(a)



(b)

100 Hz



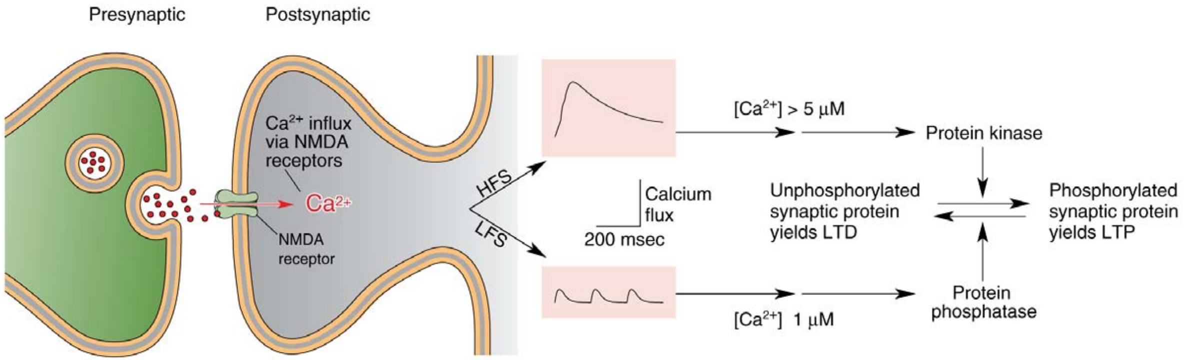
(b)

20 Hz

What is the difference ?

1Hz – no change
20 Hz – depression
100 Hz – potentiation

Calcium influx can modulate synaptic strength in both directions



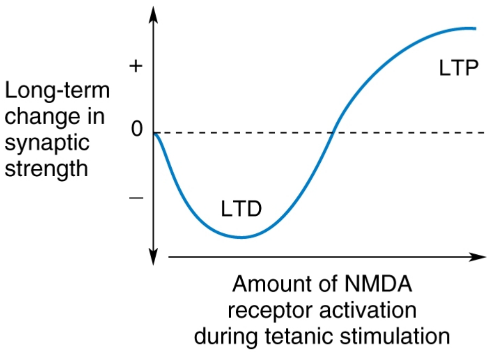
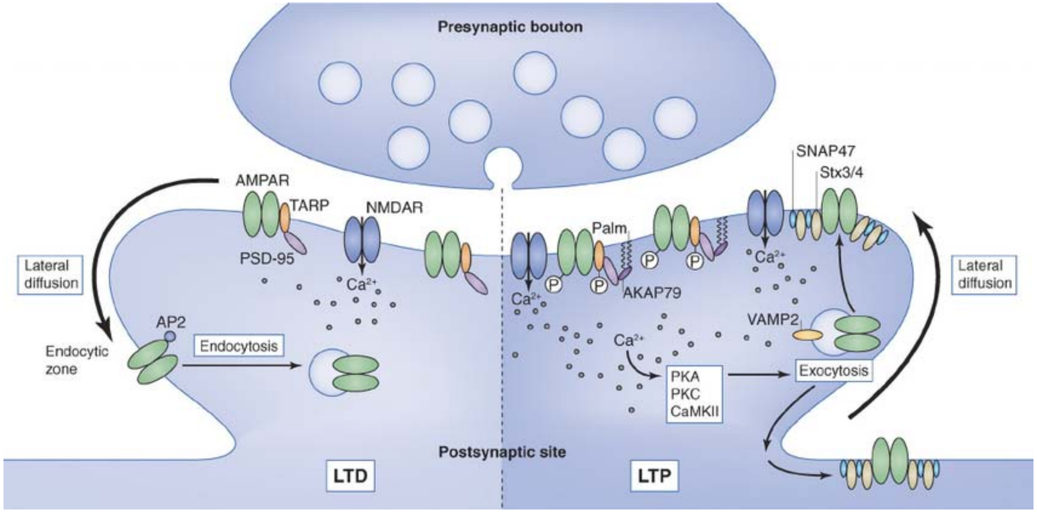


Figure 25.14

Calcium influx can modulate synaptic strength in both directions



https://www.researchgate.net

(1) activation of NMDAR promotes Ca 2+ influx, which is followed by
(2) activation of kinases (PKC, PKA, and CaMKII),
(3) phosphorylation of GluA1-containing AMPARs,
(4) triggering of their exocytosis from intracellular pools.
(5) Palmitoylation (Palm) of AKAP79/150 promotes AMPAR trafficking and surface delivery. AMPAR exocytosis is mediated by members of the SNARE complex that differ from the ones that regulate presynaptic release. (Left)
(6) Long-term depression (LTD) is induced by a moderate level of Ca 2+ influx and is characterized by the endocytosis of AMPAR from synapses.
(7) AMPAR are linked to clathrin via AP2. AKAP79/150 is depalmitoylated and removed from dendritic spines.

You DON'T need to know these details

Clicker question

Influx of Acetylcholine (ACh) during a task involving attention raises the membrane voltage of a postsynaptic neuron by 10 mV. This can happen because

A. ACh closes usually open K+ channels
B. Activates an inhibitory synapses increasing permeability to CL-
C. Closes usually open Na+ channels
D. None of the above

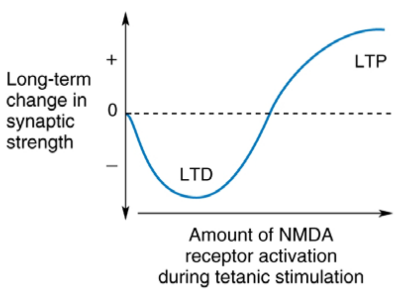
Clicker question

Influx of Acetylcholine (ACh) during a task involving attention raises the membrane voltage of a postsynaptic neuron by 10 mV. This can happen because

A. ACh closes usually open K+ channels
B. Activates an inhibitory synapses increasing permeability to CL-
C. Closes usually open Na+ channels
D. None of the above

Influx of ACh raises the membrane voltage by 10 mV. This results in stimulation frequency needed to obtain LTP versus LTD to be ------ than in the absence of ACh

A. Lower
B. Higher



The presence of ACh has been shown to lead to an increase in synaptic plasticity during learning. This could be due to

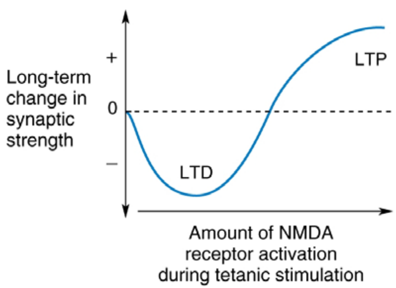
A. Depolarization of the postsynaptic membrane voltage
B. Increased excitability of the presynaptic cell
C. Increased Ca+ influx through NMDA receptor
D. All of the above
E. None of the above

Clicker question

A)

B)

C)



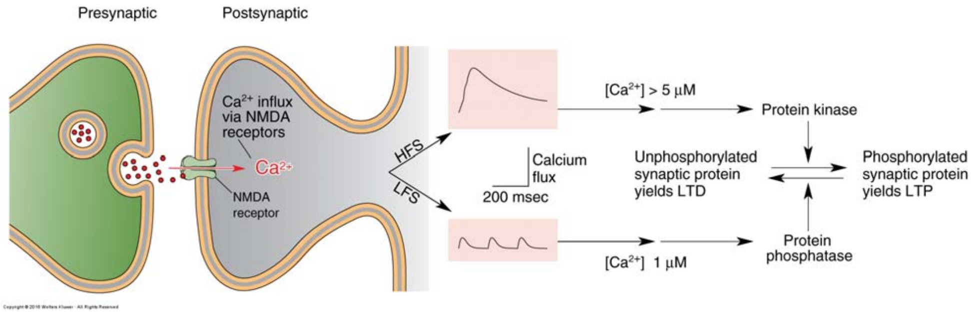
The presence of ACh has been shown to lead to an increase in synaptic plasticity during learning. This could be due to

A. Depolarization of the postsynaptic membrane voltage
B. Increased excitability of the presynaptic cell
C. Increased Ca+ influx through NMDA receptor
D. All of the above
E. None of the above

Clicker question

Short term synaptic facilitation can affect LTP and LTD

A. True
B. False



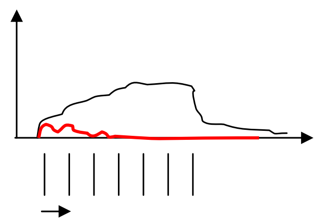
Clicker question

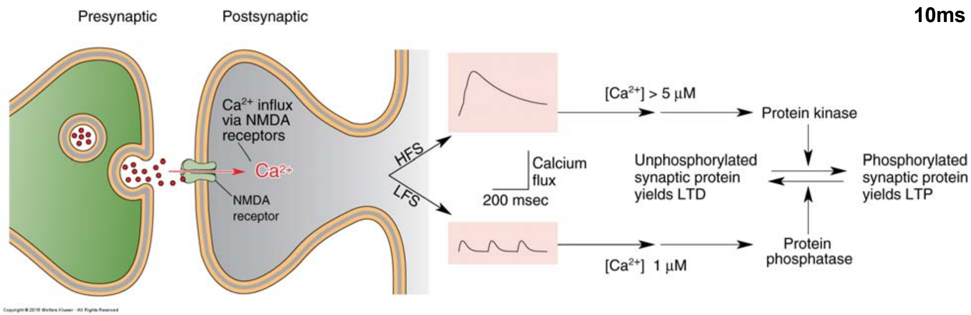
Short term synaptic facilitation can affect LTP and LTD

A. True
B. False

A modulator changes a synapse with no short term plasticity into a synapse with strong synaptic depression. When stimulated at 100 Hz, this synapses now

A. Undergoes LTP
B. Undergoes LTD
C. Does not change





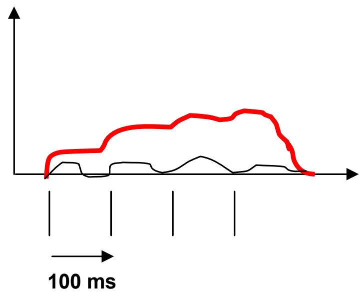
Clicker question

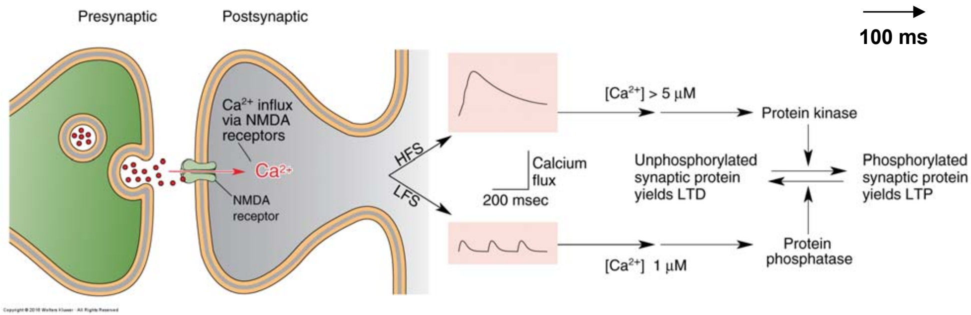
Short term synaptic facilitation can affect LTP and LTD

A. True
B. False

A modulator changes a synapse with no short term plasticity into a synapse with strong synaptic facilitation. When stimulated at 10 Hz, this synapses now

A. Undergoes LTP
B. Undergoes LTD
C. Does not change





Case study: is LTP involved in learning?

What type of experimental evidence would convince you that LTP/LTP are involved in a specific learning paradigm?

Case study: is LTP involved in learning?

An number of observations suggest that LTP/LTD may be involved in learning in the behaving animal:

- LTP can be obtained by electrical stimulation in *in vivo* preparations as well as in behaving animals

- animals in which NMDA receptors have been blocked are impaired in certain tasks (water maze, radial maze)

- genetically engineered mice which have no NMDA receptors in the hippocampal formation CA1 are impaired in spatial learning tasks

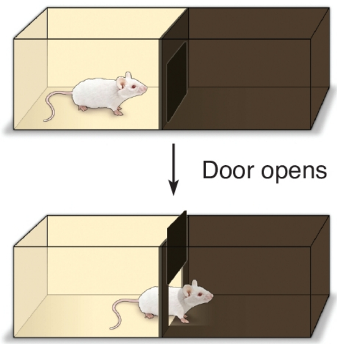
- pyramidal cells in the hippocampus of these mice have less precise receptive fields

- neuromodulators like acetylcholine enhance LTP formation in brain slice experiments; cholinergic antagonists impair learning in many behavioral experiments

- a study using electrical stimulation of the olfactory bulb as cues for electrical stimulation found potentiation of the evoked EPSP's ONLY for stimulations paired with a reward.

and many more ..

Case study: is LTP involved in learning?
Inhibitory avoidance learning



Clicker question:

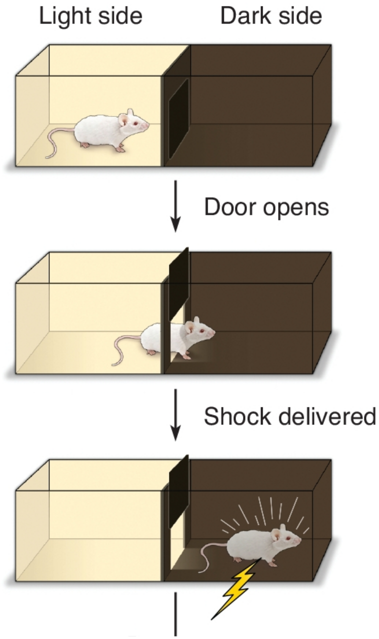
Mice are nocturnal. Left to their own device, they will choose to spend time in the

A. Dark
B. Light

side of the box.

Figure 25.17

Case study: is LTP involved in learning?
Inhibitory avoidance learning



Clicker question:

Mice are nocturnal. Left to their own device, they will choose to spend time in the

A. Dark
B. Light

side of the box.

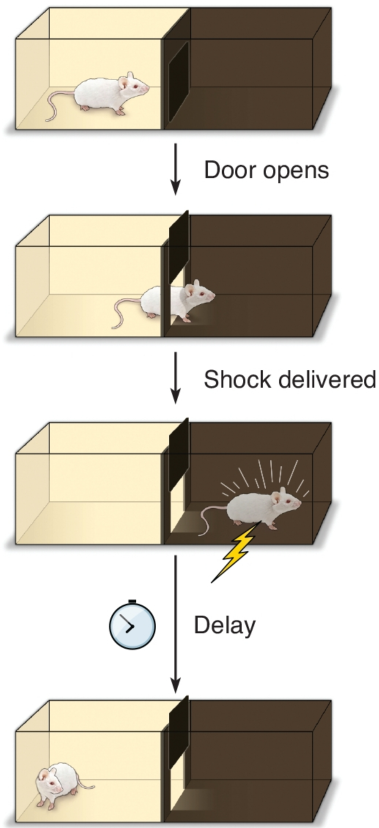
If the shock is associated with the dark side they will spend

A. More
B. Less

time on that side

Figure 25.17

Case study: is LTP involved in learning?
Inhibitory avoidance learning



(a)

Clicker question:

Mice are nocturnal. Left to their own device, they will choose to spend time in the

A. Dark
B. Light

side of the box.

If the shock is associated with the dark side they will spend

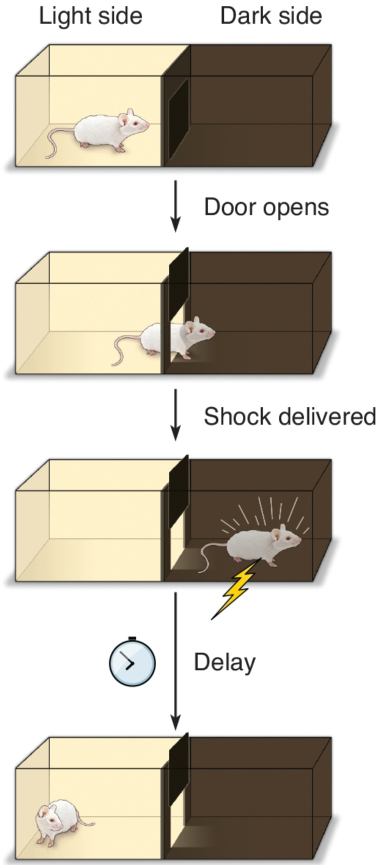
A. More
B. Less

time on that side

After a delay, the delay to entry of dark side is measured to give an indication of learning the association between shock and dark side

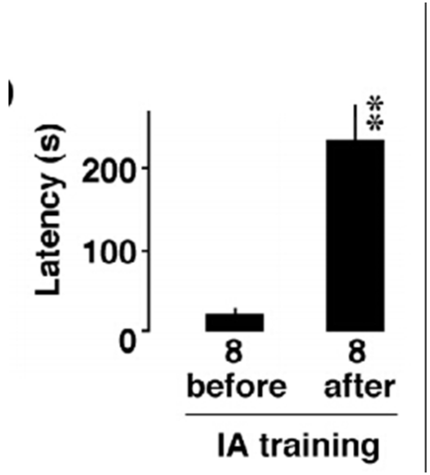
Figure 25.17

Case study: is LTP involved in learning?
Inhibitory avoidance learning



(a)

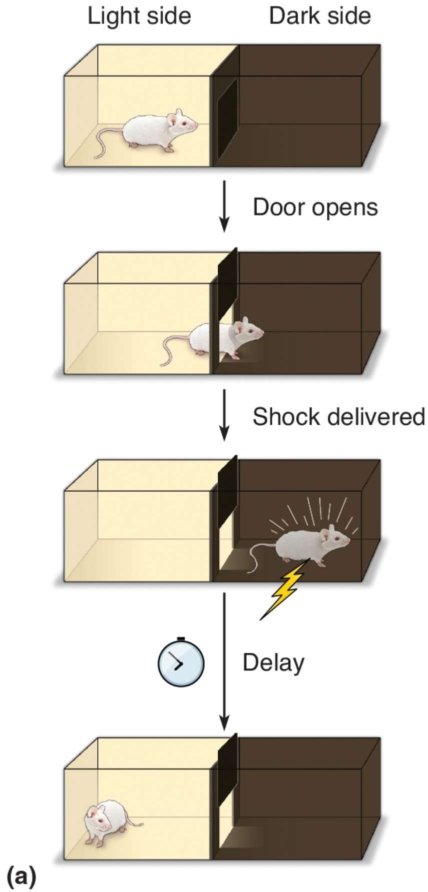
This paradigm creates wide spread activation in a brain area called the hippocampus. This area is thought to be involved in creating a memory trace.
Hint: LTP was first discovered in the hippocampal formation.



After a delay, the delay to entry of dark side is measured to give an indication of learning the association between shock and dark side

Figure 25.17

Case study: is LTP involved in learning?
Inhibitory avoidance learning



This paradigm creates wide spread activation in a brain area called the hippocampus. This area is thought to be involved in creating a memory trace.
Hint: LTP was first discovered in the hippocampal formation.

Brainstorm: what experiment(s) could you perform to test the hypothesis that LTP in the hippocampus is involved?

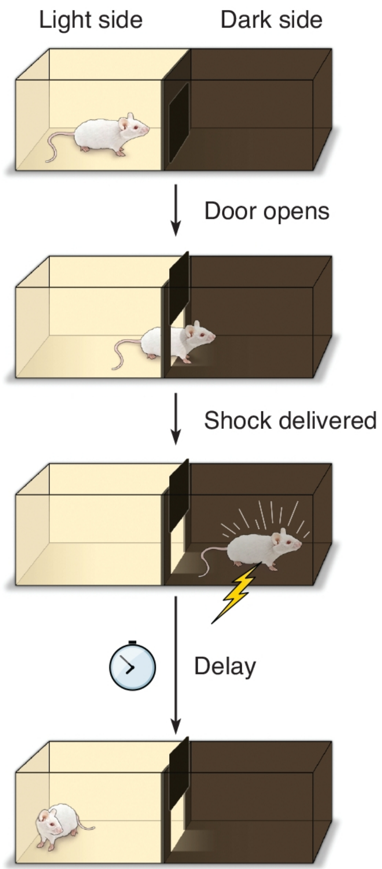
Figure 25.17

Clicker question

It is generally believed that LTP needs functioning NMDA receptors. A “blocker” of NMDA receptors infused into a brain will

A. Prevent Mg+ to be released from the synapse
B. Bind to the receptor but prevent entry of Ca+ and Na+
C. Hyperpolarize the cell
D. Bind to the receptor and open it

Case study: is LTP involved in learning?
Inhibitory avoidance learning



(a)

This paradigm creates wide spread activation in a brain area called the hippocampus. This area is thought to be involved in creating a memory trace.
Hint: LTP was first discovered in the hippocampal formation.

Experiment 1: Infusion of NMDA blockers

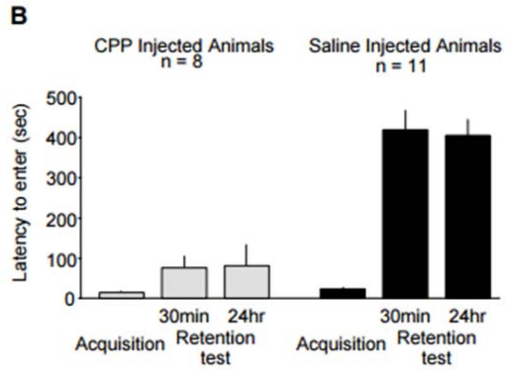
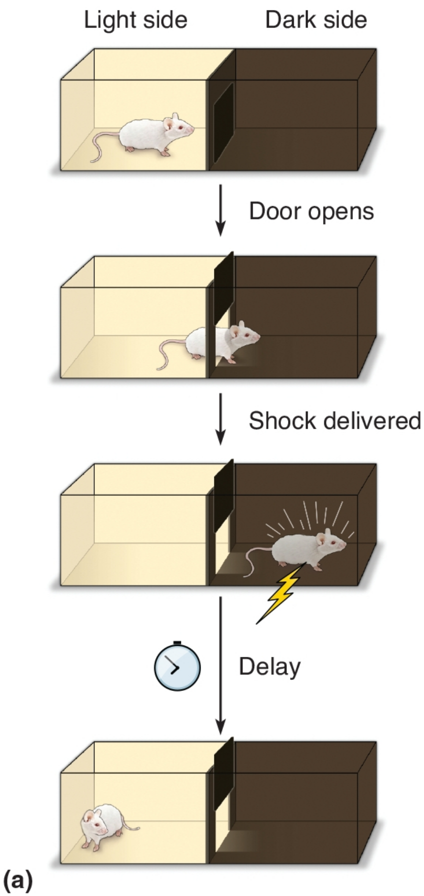


Figure 25.17

Case study: is LTP involved in learning?
Inhibitory avoidance learning



This paradigm creates wide spread activation in a brain area called the hippocampus. This area is thought to be involved in creating a memory trace.
Hint: LTP was first discovered in the hippocampal formation.

Experiment 2: Recording synaptic potentials in the hippocampus

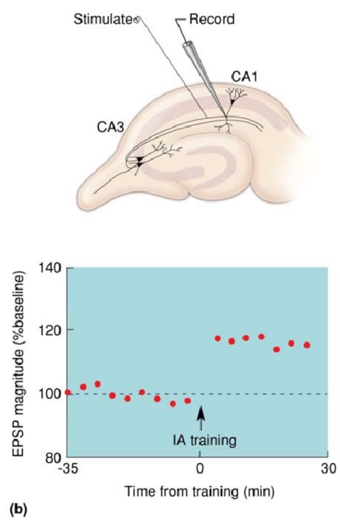


Figure 25.17

What you should take away from this lecture and remember

(1) Long term depression and long term potentiation can be experimentally induced by stimulating presynaptic fibers at different frequencies
(2) Ca+ entry into the postsynaptic cell can induce both LTP and LTD
(3) Levels of Ca+ entering the cell determine the direction of plasticity
(4) Intracellular molecular cascades in response to Ca+ regulate insertion of delation of AMPA receptors
(5) LTP and LTD can be modulated by other substances such as Acetylcholine because these modulate cell excitability, short term plasticity and membrane voltage
(6) LTP/LTD have been associated with learning in awake behaving animals
(7) There are a number of experimental paradigms that can be used to test if LTP/LTD at a specific synapse are involved in learning