Brain Science Fundamentals

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Part 12: Mechanisms of Learning and Plasticity in Neurons

Reading: Bear, Connors, and Paradiso, Chapters 23 and 25

Most of the material for this section comes from chapter 25, but some is from the end of chapter 23.

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Different Types of Learning and Memory

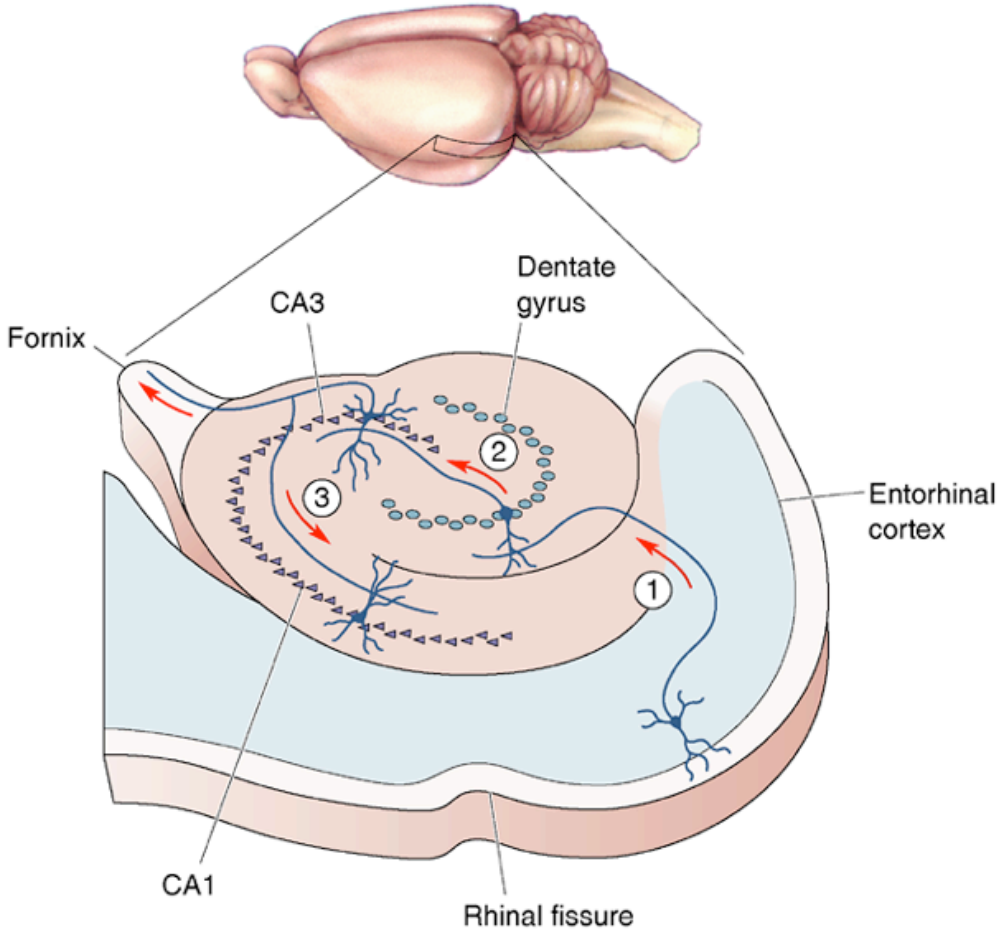
- Multiple types of learning and memory are distinguished
  - The distinctions are largely at a psychological level. They are based upon the sort of information and whether or not it reaches consciousness
  - These distinctions are covered in chapter 24
  - I do not think they are of fundamental importance to neurobiology, so we will not cover these topics
- Learning and memory occurs in each neuron of the nervous system
- Most of it never reaches consciousness
- The principles of information processing do not depend on the type of information or whether it reaches consciousness

Model Synapses for the Study of Associative Plasticity

- Hippocampus (Schaffer collaterals to CA1 synapse)
  - This is the best studied synapse. Glutamate is the transmitter, and it is a model for many vertebrate synapses.
  - The hippocampus is important for formation of conscious, high-level, cognitive memories
  - Unfortunately, it is very difficult to relate hippocampus to sensory input or motor output. Circuitry is poorly understood.
- Cerebellum (parallel fiber to Purkinje cell synapse)
  - Relative to HC, closer to sensory and motor, and better understood circuitry
  - But still not very well understood circuitry and relationship to behavior
- Aplysia and other invertebrates
  - Simple and well understood circuitry
  - Simple relationship of synaptic plasticity to sensory input and motor output

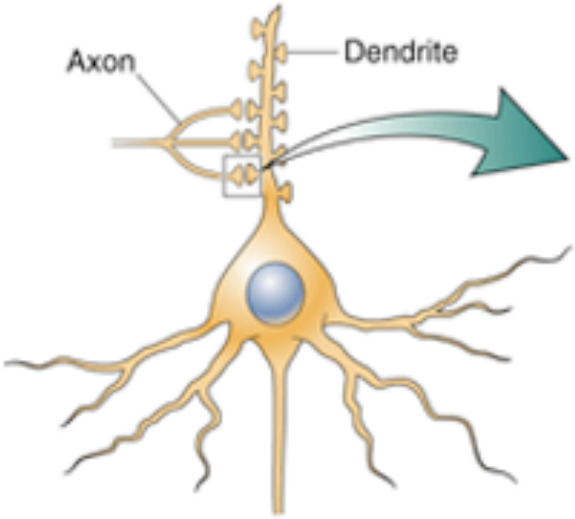
Hippocampus

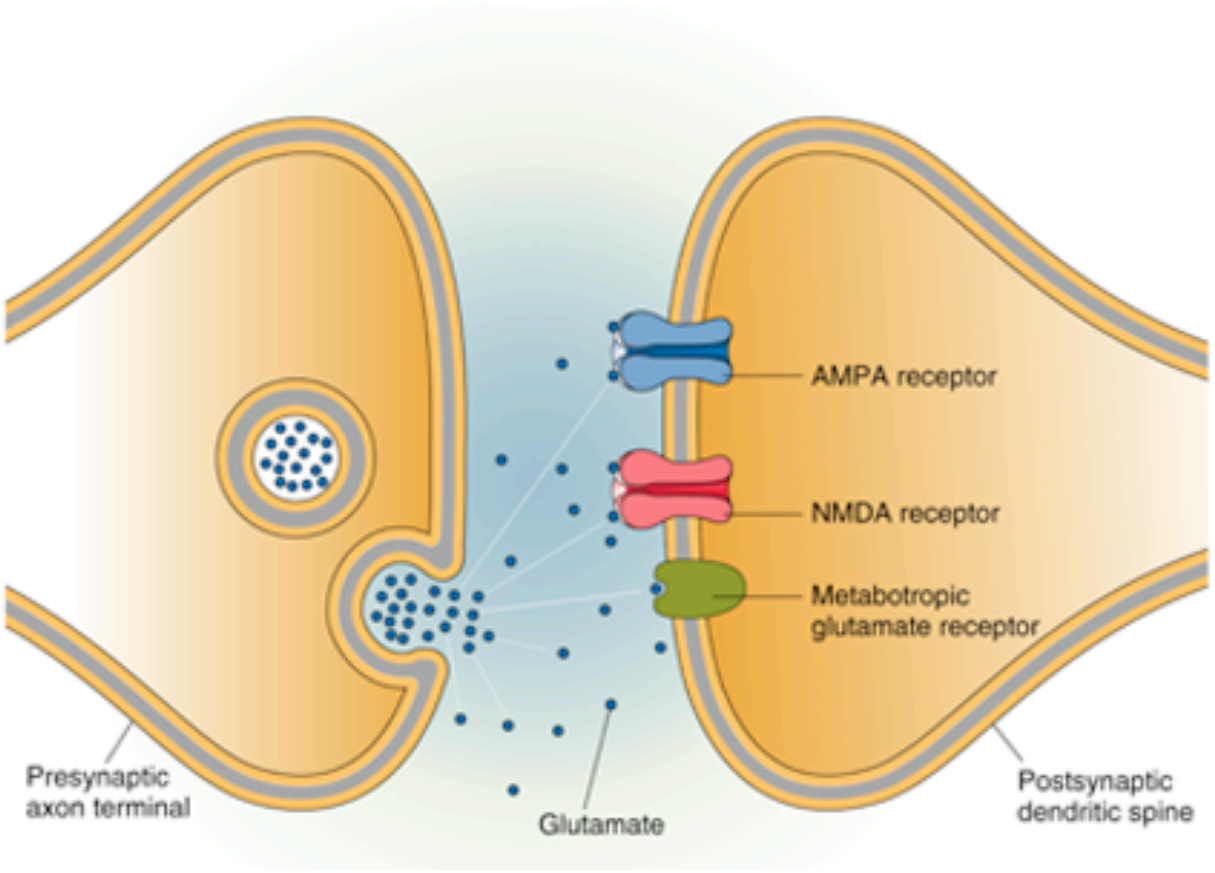
- HC is important for the formation of declarative (conscious) memories
- The CA3 to CA1 synapse is the classical synapse to study synaptic plasticity



Glutamate Synapses

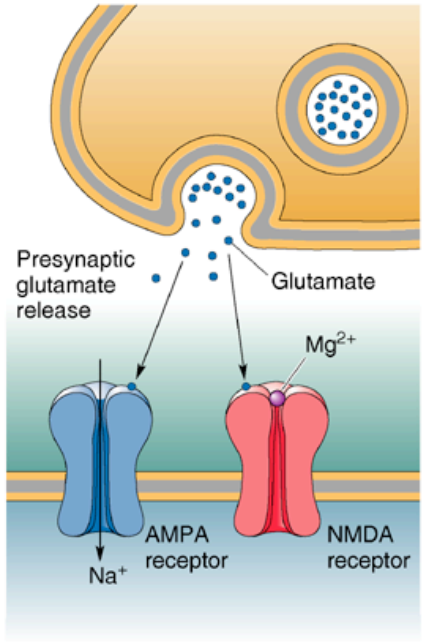
- 3 types of glutamate receptors:
  - AMPARs: fast glutamate-gated ion channels
  - NMDARs: glutamate-gated ion channels with unique properties
  - mGluRs: slow G-protein coupled transduction



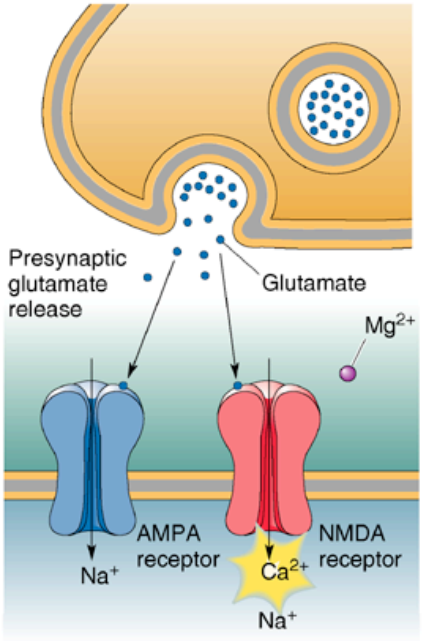


NMDA Receptors

- Special Properties of NMDA Receptors
  - ➢ Voltage-gated ion channel
    - Mg2+ block (different from other voltage-gated channels)
  - ➢ Coincidence-detector
    - Glutamate + depolarization
    - Pre + post-synaptic activity
  - ➢ Calcium-permeable
  - ➢ Slower than AMPA receptor
    - AMPAR receptor releases glutamate almost instantly (<1 ms)
    - NMDAR releases glutamate more slowly (~100 ms)
    - Thus NMDA receptor stores a trace of recent presynaptic activity



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



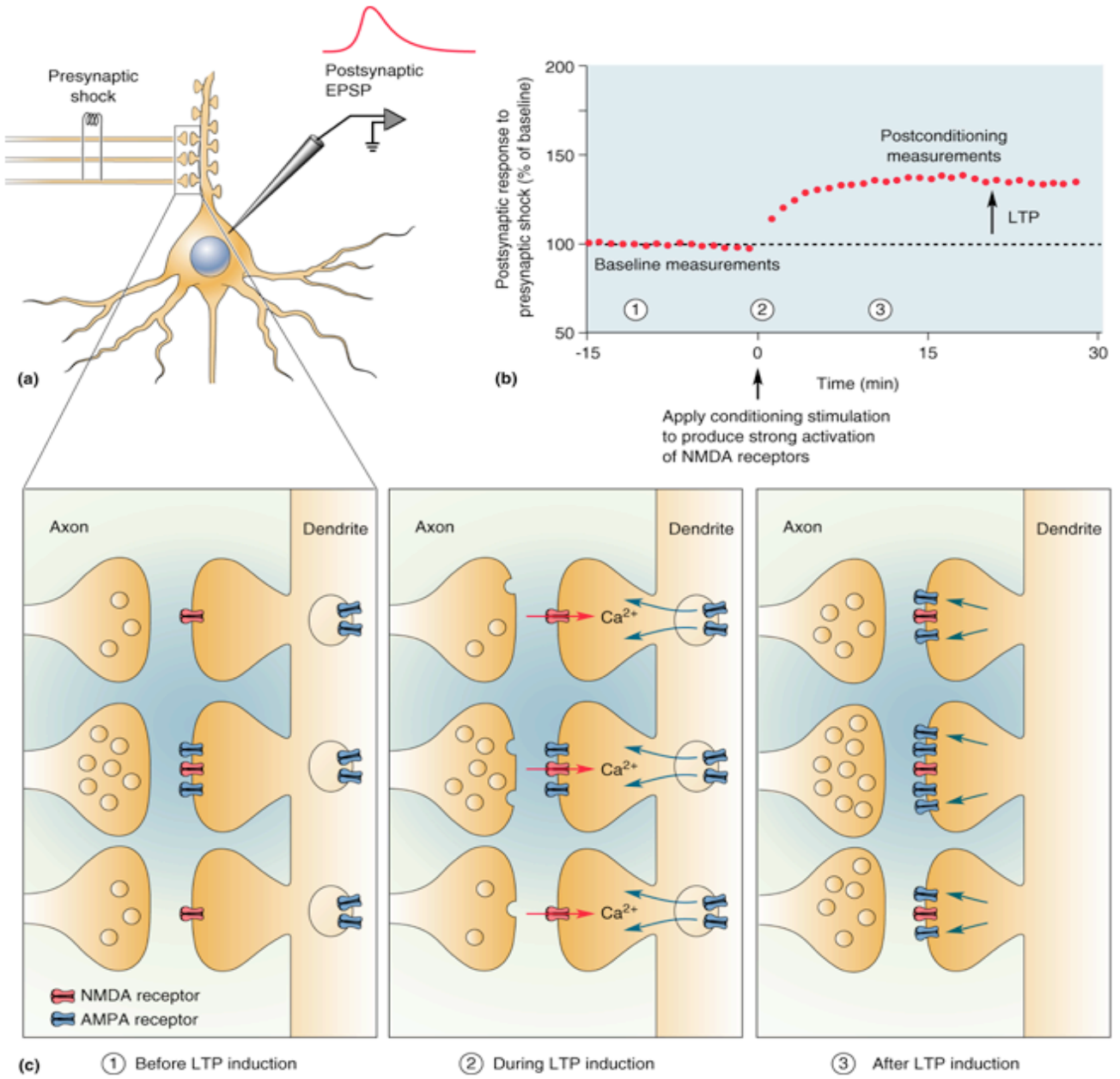
(b) Postsynaptic membrane at **depolarized** potential

Long-Term Synaptic Potentiation (LTP) and Depression (LTD)

- LTP (LTD) is a long lasting potentiation (depression) of synaptic strength (or weight)
  - Experimental tests
    - Monitor synaptic strength before and after episodes of strong NMDAR activation
    - LTP induction protocols
      - High frequency stimulation
      - Low frequency stimulation paired with postsynaptic depolarization
      - Spike timing dependent plasticity (pre before post causes LTP)
  - Main expression mechanism is the insertion or removal of AMPA-type glutamate receptors
  - NMDA receptor: induction of plasticity
  - AMPA receptor: expression of plasticity

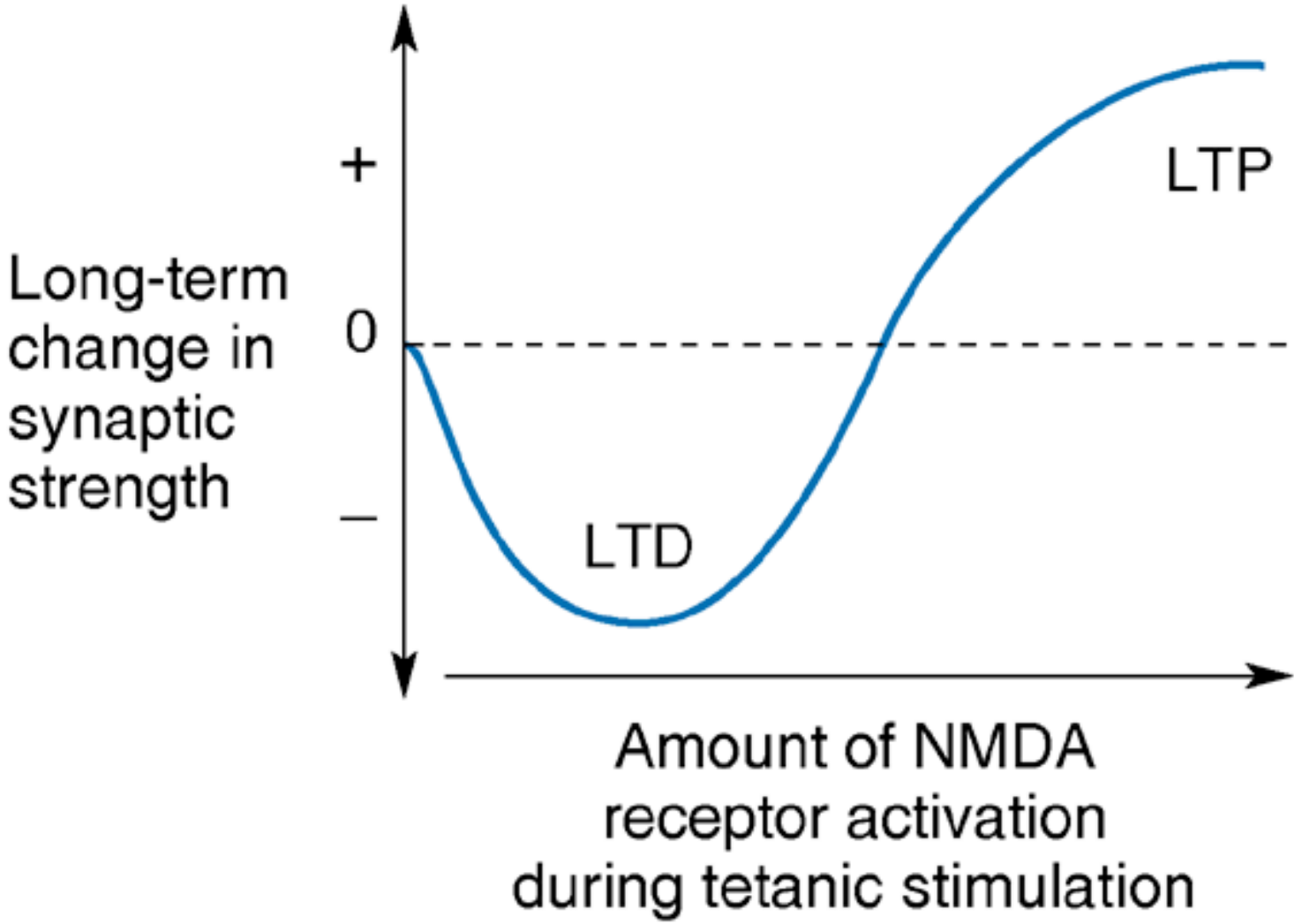
Long-Term Potentiation

Long-Term Potentiation (LTP) of synaptic strength is caused by the opening of NMDA channels, which causes an increase in postsynaptic [Ca2+].



Long-Term Potentiation and Depression

- LTP is caused by strong activation of NMDA receptors and high [Ca2+] in the postsynaptic spine.
- LTD is caused by weak activation of NMDA receptors and moderate [Ca2+] in the postsynaptic spine.

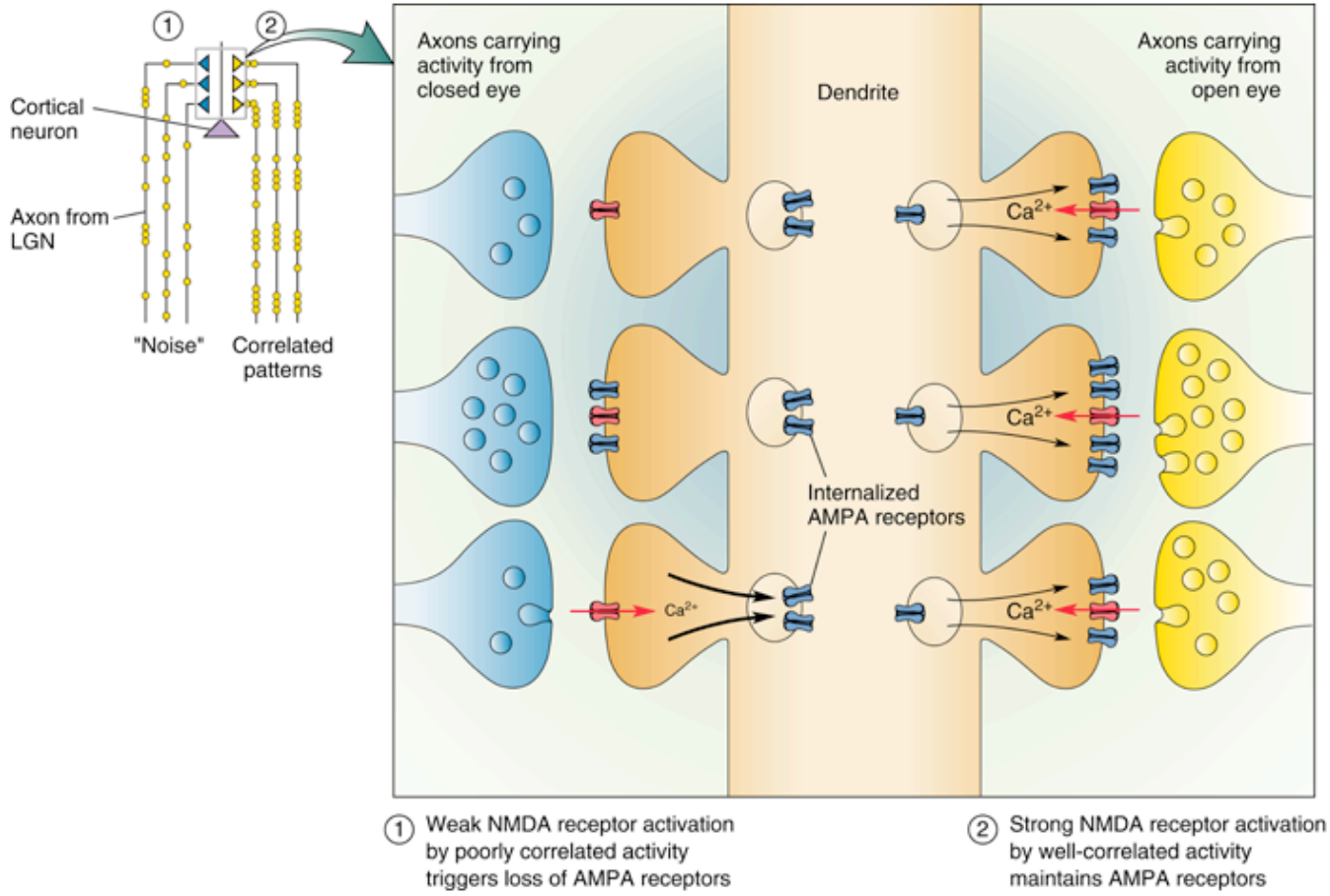


LTP and LTD (continued)

- "Silent synapses"
  - NMDA receptors only (weight near zero)
- AMPA receptors can be added to increase weight (or strength)
- Calcium influx through NMDA is the learning signal (indicates coincidence of pre and postsynaptic activity)
  - High calcium causes LTP (increase in weight)
  - Low calcium causes LTD (decrease in weight)
    - LTD requires presynaptic activity with low postsynaptic activity. This causes a small elevation of calcium above its very low baseline level.
- Information transmission mechanism (AMPA) is independent from learning mechanism (NMDA)

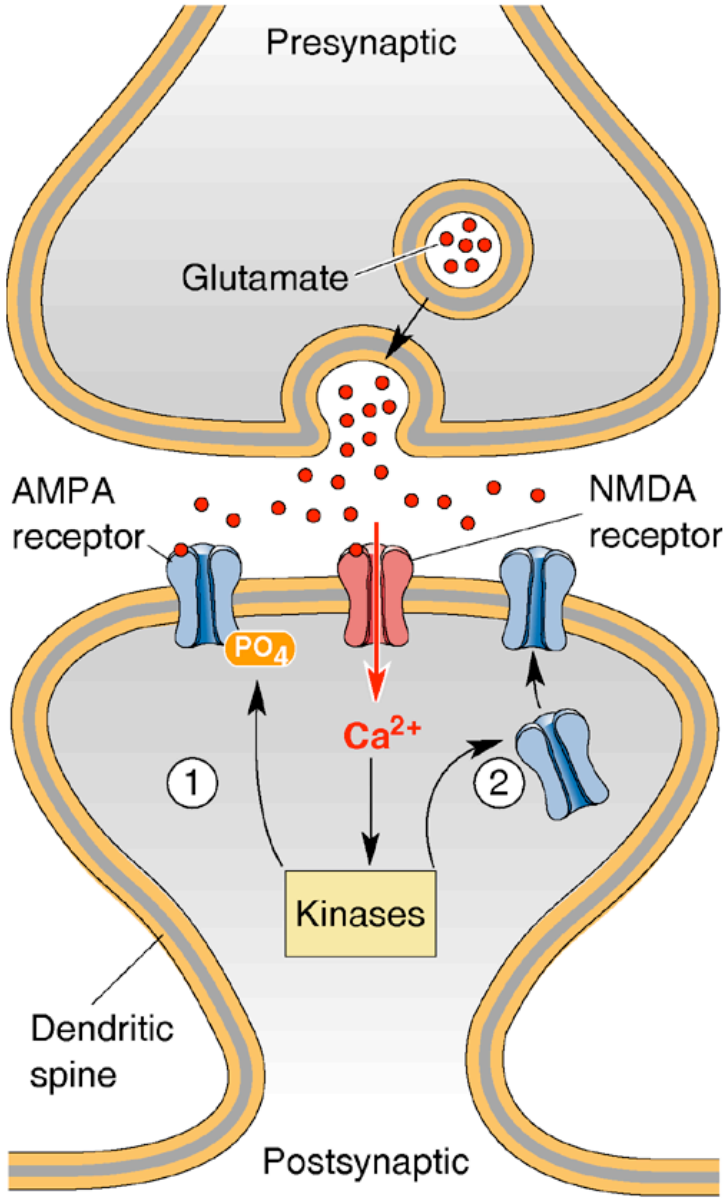
Mechanism of plasticity following monocular deprivation

- Well correlated synaptic activity from open eye causes strong Ca2+ influx through NMDA receptors (LTP, high weight)
- Uncorrelated synaptic activity from closed eye causes weak Ca2+ influx (LTD, low weight)
- LTD may eventually lead to a complete loss of synapses



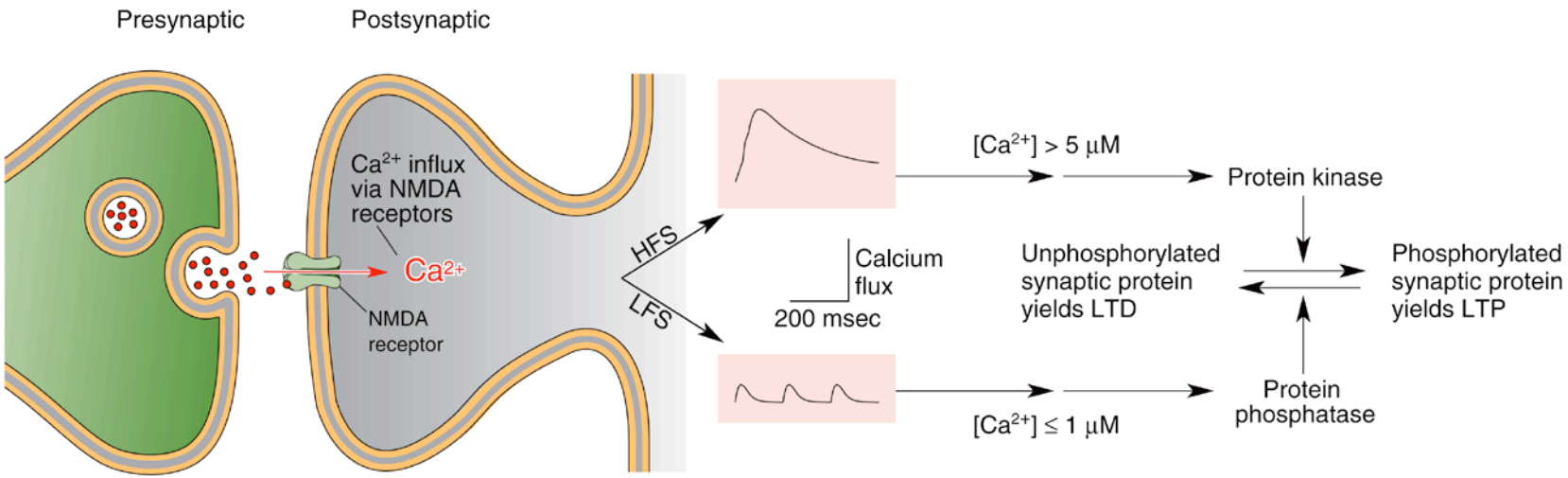
Mechanism of LTP in HC CA1

- Coincidence of pre + postsynaptic activity causes calcium to enter through NMDA receptors
- Calcium activates kinases
- Phosphorylation of AMPA receptors enhances responsiveness to glutamate
- Phosphorylation of various proteins also leads to insertion of AMPA receptors to membrane
- A low level of calcium entry through NMDA receptors can activate phosphatases and cause LTD



LTP and LTD are both triggered by Ca2+

- NMDAR activation causes large rise in [Ca2+] during depolarized periods
  - ➢ High [Ca2+] activates kinases
  - ➢ Add AMPA receptors to membrane
- NMDAR activation causes a small rise in [Ca2+] during more hyperpolarized periods
  - ➢ Low [Ca2+], but greater than baseline, activates phosphatases
  - ➢ Phosphatases remove phosphate groups from proteins
  - ➢ AMPA receptors are ultimately removed from membrane



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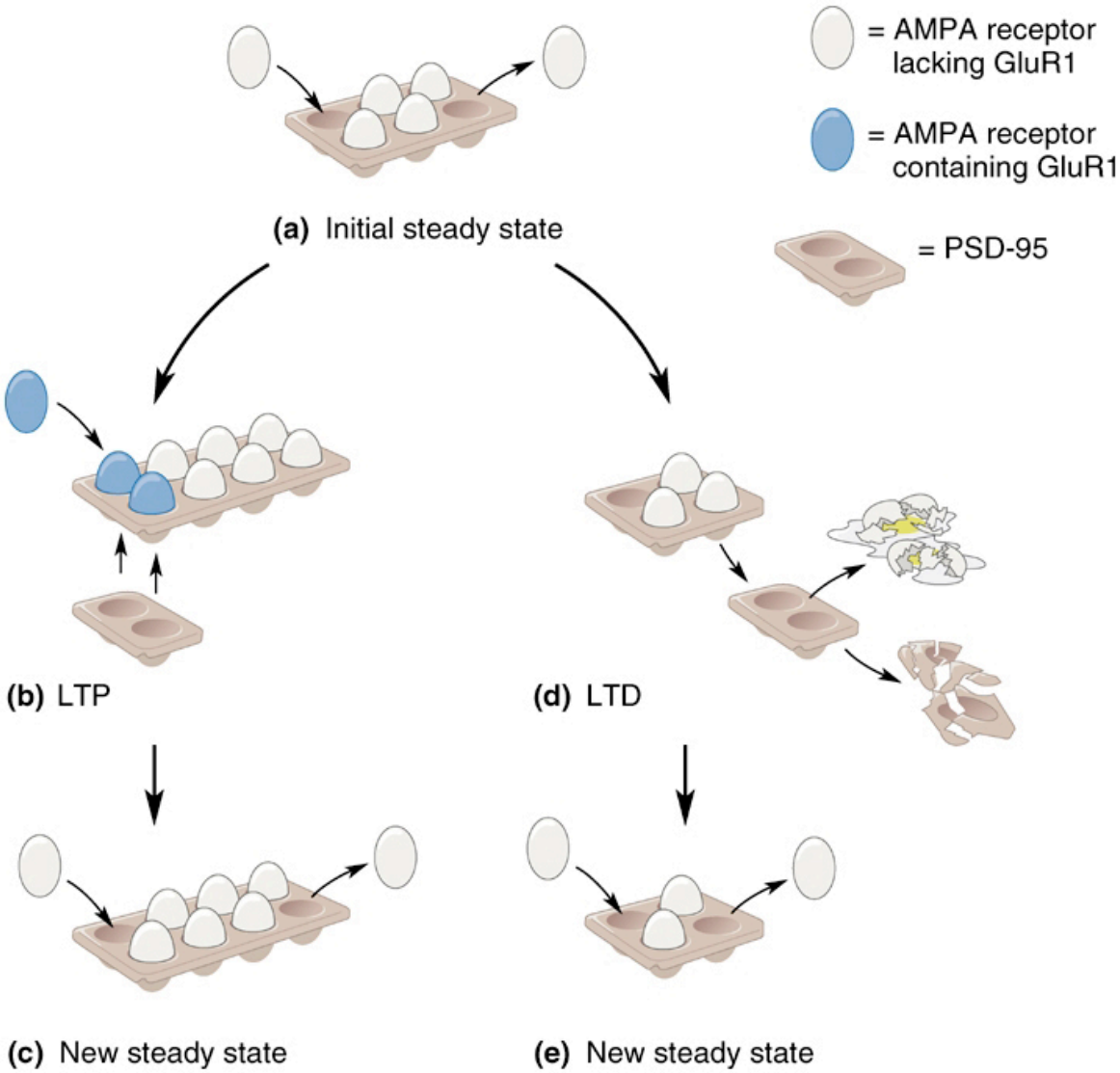
"Egg Carton Model" of AMPA receptor Trafficking in LTP and LTD

- AMPA receptors are held in place by PSD-95 and other scaffold proteins
- The scaffold holds the AMPA receptors in the membrane, like an egg carton holds eggs
- LTP (LTD) increases (decreases) the size of the scaffold
  - Thus, more AMPA receptors are inserted (removed)
  - New AMPA receptors contain the subunit GluR1

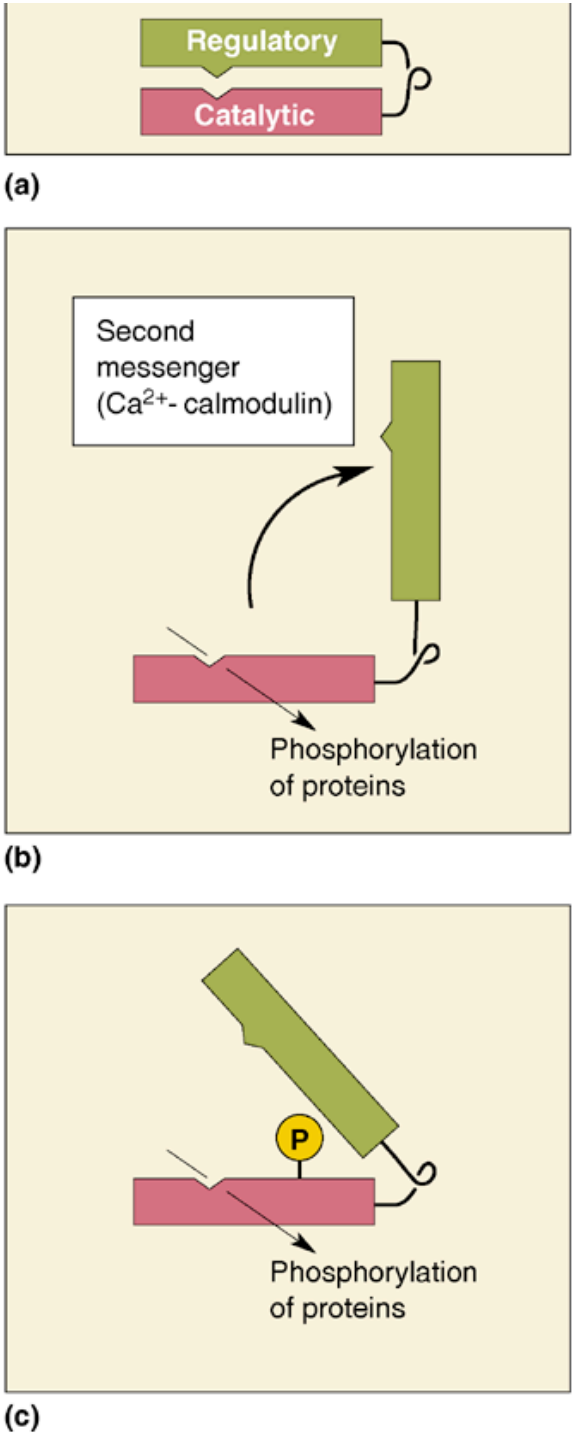


Mechanisms of Plasticity over Multiple Timescales

- Phosphorylation and Dephosphorylation
  - Seconds to minutes
  - Other protein modifications
- Ion Channel insertion or removal
  - Minutes to Hours
- Changes in Gene Expression
  - Hours to Years
  - Changes in synaptic strength that last more than about 2 hours require changes in gene expression and protein synthesis
- New Synapses Can Form

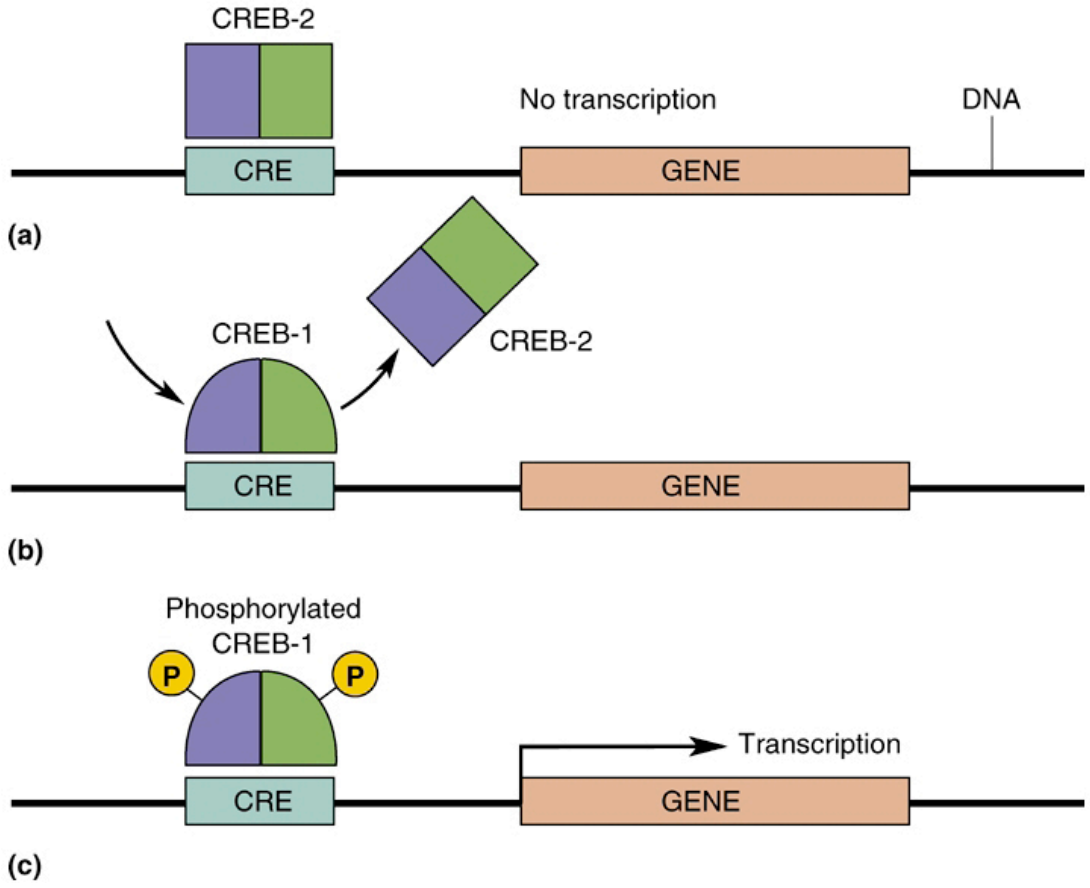
The Molecular Basis of Long-Term Memory

- Phosphorylation alone is not sufficient for long-term memory
  - ➢ It may last for seconds to minutes
- Persistently Active Protein Kinases
  - ➢ Auto-Phosphorylation induced by calcium causes CaMKII to stay "on"
  - ➢ As long as CaMKII is activated, it keeps its substrate proteins (such as AMPA receptors) phosphorylated



Changes in Gene Expression

- Very long lasting changes (> 2 hours) in synaptic strength require changes in gene transcription and translation
  - When cyclic AMP response element binding protein 2(CREB-2) is bound to CRE, downstream genes are not transcribed
  - When CREB-1 is bound to CRE, and it is phosphorylated by protein kinase A (PKA), then transcription is activated.
  - PKA can be activated during conditioning that causes LTP



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Limitations of Conventional LTP and LTD

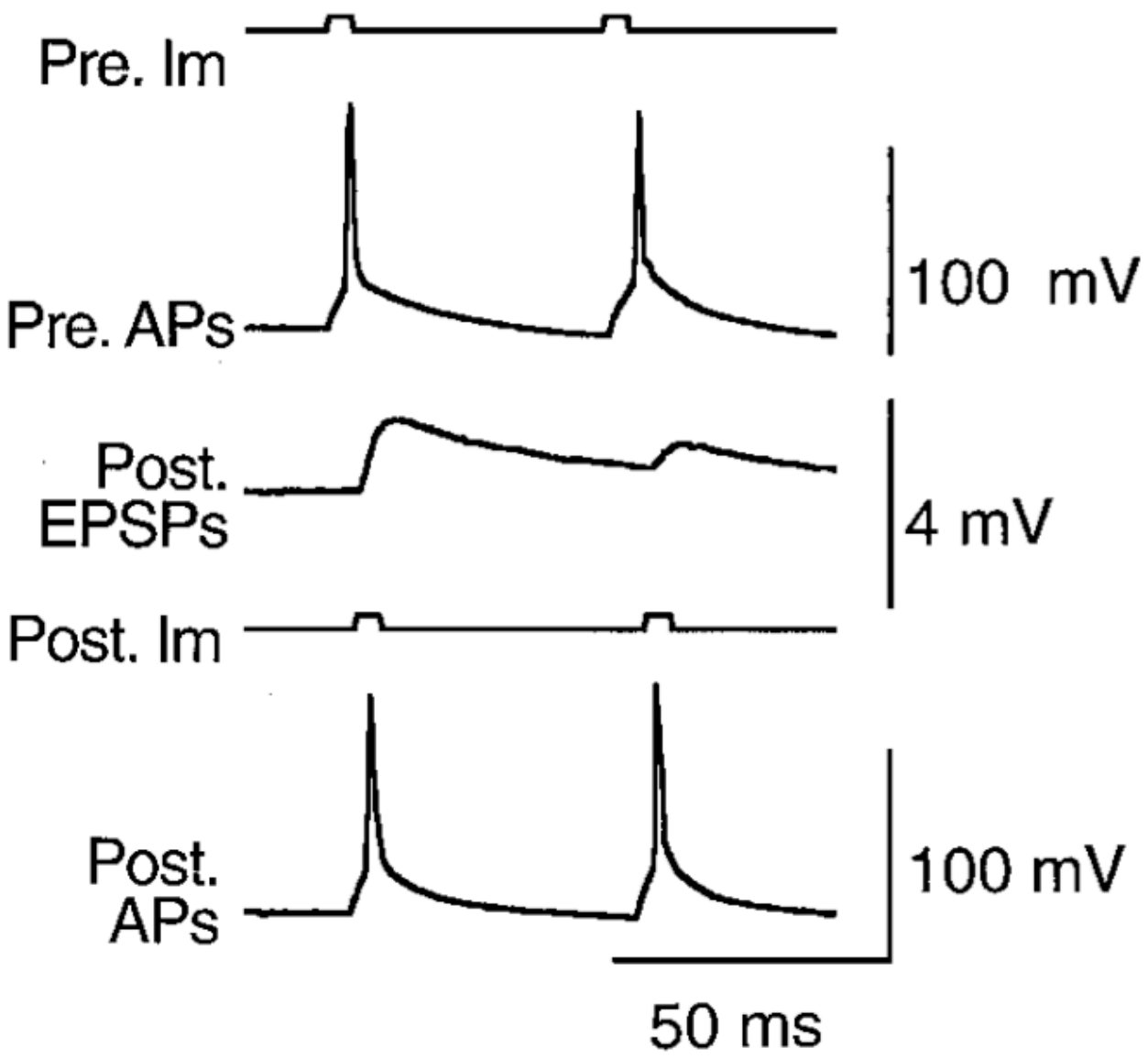
- LTP is usually induced by high frequency presynaptic activity, and LTD by low frequency activity
- These conditioning methods may not be physiologically relevant
- The important computational principle in Hebbian plasticity is that presynaptic activity should contribute to (or "cause") postsynaptic activity
  - This means that presynaptic activity should occur before postsynaptic activity
- "Spike timing dependent plasticity" is more physiological and follows Hebb's original proposal more precisely than conventional LTP
  - See box 25.1 on page 782

Spike Timing Dependent Plasticity (STDP)

- If an EPSP at a synapse contributes to causing an action potential (AP), then the EPSP should occur before the AP
  - This is because of the conduction delay, which is especially long if the EPSP occurs far out on a dendrite
- If an AP occurs before an EPSP, then that probably means that another EPSP caused the AP
  - If one synapse tends to be active before a second synapse, then the first one is more valuable because it predicts the second. The first one should become strong and the second one weak.
- In the most common form of STDP at excitatory synapses, pre (EPSP) before post (AP) causes potentiation, and post before pre causes depression of synaptic strength
  - This is a Hebbian rule
  - The opposite rule (anti-Hebbian) has been observed at some synapses
- The mechanisms of STDP may be the same as for conventional LTP and LTD

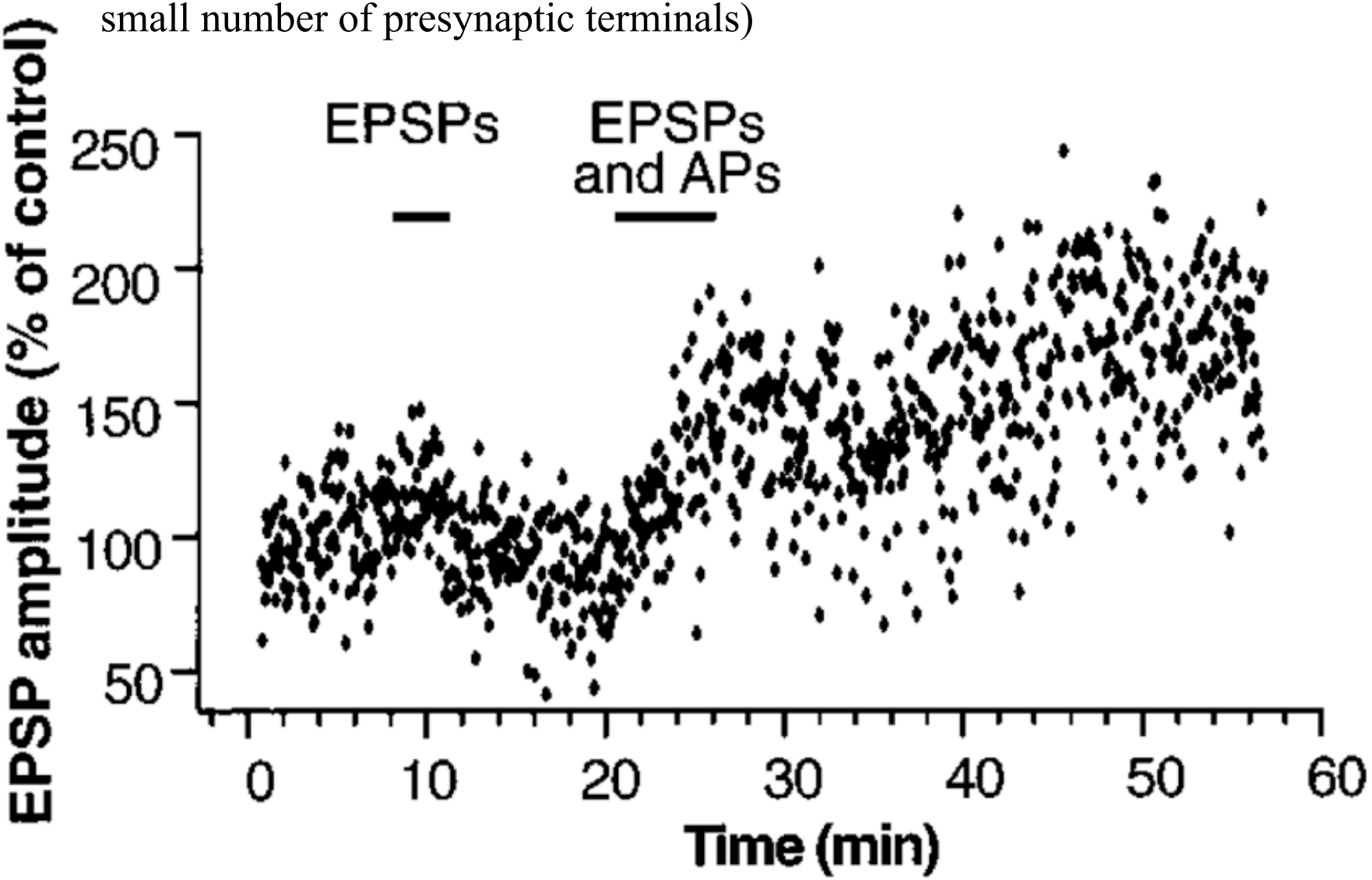
Spike Timing Dependent Plasticity (STDP)

An experiment with 2 intracellular electrodes, one in the presynaptic neuron, and one the in the postsynaptic neuron. Current is injected to cause presynaptic APs and postsynaptic EPSPs. The EPSPs do not cause postsynaptic APs. But current is injected into the postsynaptic neuron to cause APs. The timing of the postsynaptic APs is controlled relative to the presynaptic APs.

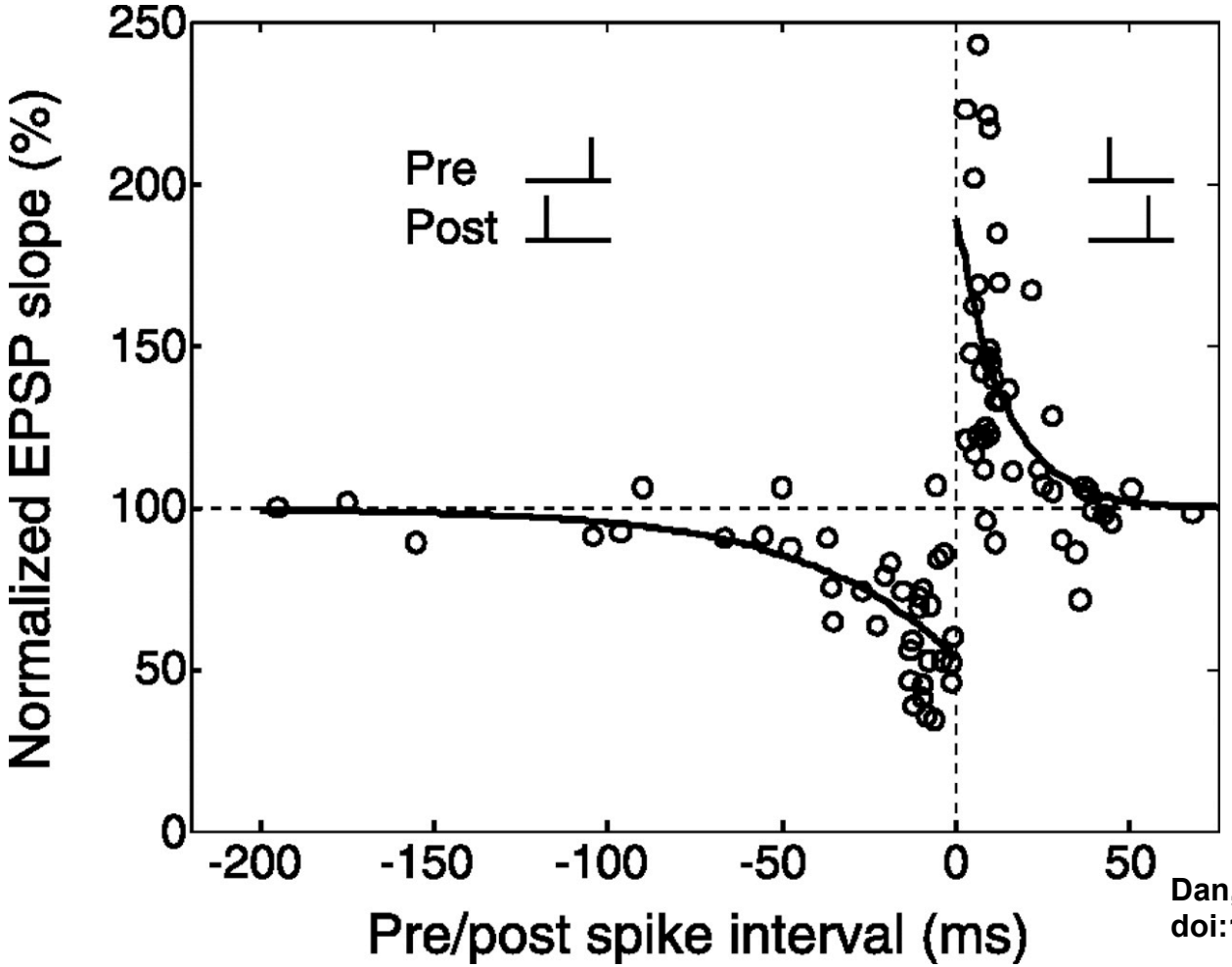


Spike Timing Dependent Plasticity (STDP)

- When EPSPs are followed by APs, synaptic strength is potentiated
- Notice that there is a lot of variability in EPSP amplitude
  - This is probably caused by variation in the number of vesicles released (from a small number of presynaptic terminals)



Potentiation and depression as a function of the interval between pre and postsynaptic spikes. Each point represents the change in EPSP size in one experiment from one neuron.



Dan, Y. et al. Physiol. Rev. 86: 1033-1048 2006;
doi:10.1152/physrev.00030.2005

FIG. 1. Synaptic modification induced by repetitively paired pre- and postsynaptic spikes in layer 2/3 of visual cortical slices from the rat

Physiological Reviews

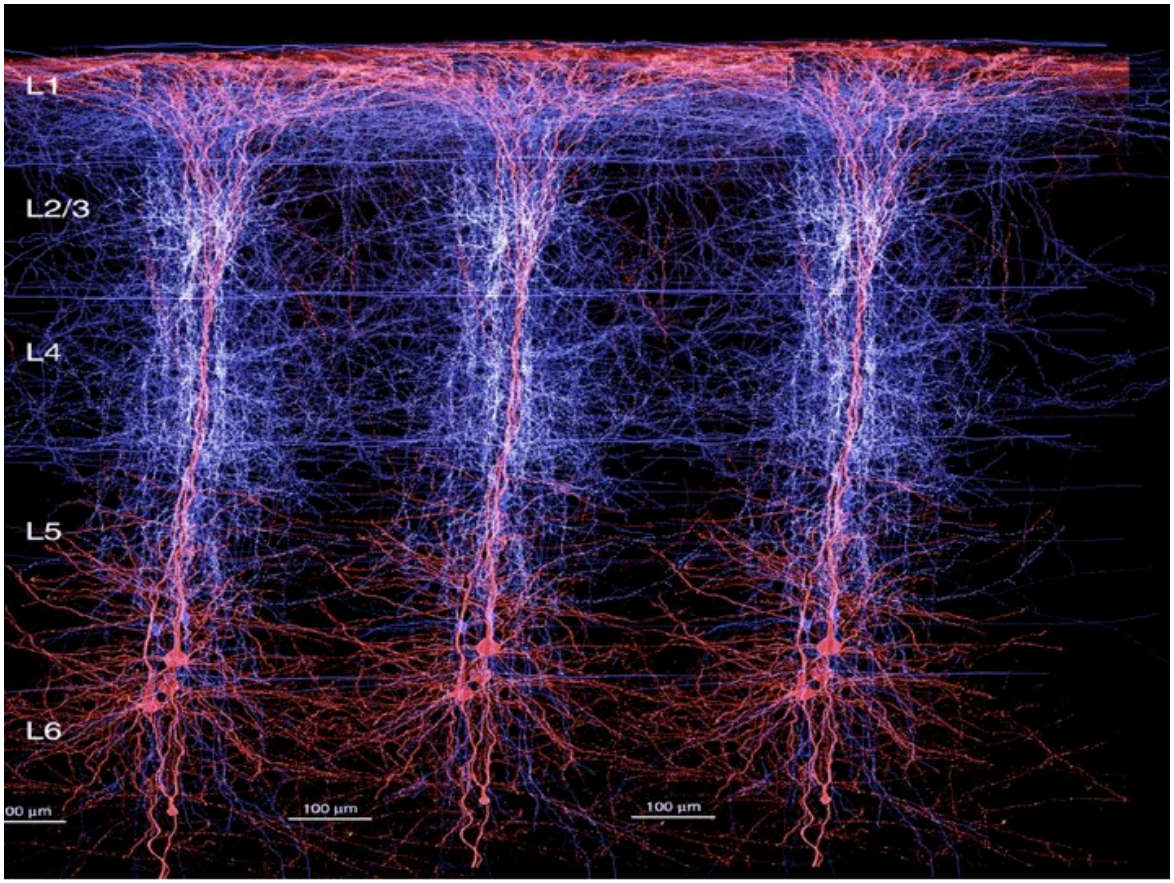
Eligibility Traces

- An eligibility trace is a “memory” of a first event that makes it eligible to be associated with a second event
- When the first event occurs, it causes an eligibility trace, which slowly decays
- When a second event occurs, it will be associated with the first event to the extent that the eligibility trace is still active
- Eligibility traces make it possible to learn a sequence of events
- STDP relies on an eligibility trace
  - An EPSP must leave a trace that allows it to be associated with an action potential that occurs later

The Eligibility Trace at a Glutamate Synapse

- Glutamate binds to NMDA receptors for about 100 ms
  - This is the eligibility trace
  - It lasts about 10 times longer than the AMPA EPSC
- If the neuron is depolarized while glutamate is bound, then the Mg2+ block of NMDA receptors will be relieved and Ca2+ will enter
- A synapse will be potentiated if presynaptic activity is followed by postsynaptic activity
- Thus the neuron can learn that activity of one presynaptic neuron predicts postsynaptic activity, and indirectly, it also predicts the activity of other synapses that tend to be active slightly later
- If synapses are activated in a sequence, then the first one to be active will be potentiated the most
  - The first one predicts the others

Cortical Pyramidal Neurons



- Dendrites can be quite long
  - The apical dendrite of a layer V or VI pyramidal neuron is about 2 mm long
- Thus there is a loss of current, and information, as an EPSP spreads passively from the synapse to the soma, especially for synapses on the distal dendrite

Dendritic Action Potentials

- Some dendrites have action potentials (DAPs)
- Unlike axonal APs, DAPs are not all-or-none and they have high thresholds
  - This is because the density of sodium channels may be less than in the axon, and K+ channel density is greater.
  - DAPs are prone to failure
    - For example, after a DAP is initiated, it could be blocked by a GABA-mediated IPSP
- DAPs propagate both forward and backward
  - Forward APs usually require large EPSPs
    - A forward DAP can be thought of as an amplification of an EPSP
  - Backward APs are reliably evoked by axonal APs
- What is the purpose of a backpropagating AP?
  - It informs the synapse that an AP has occurred in the axon

STDP and Transmission Delays

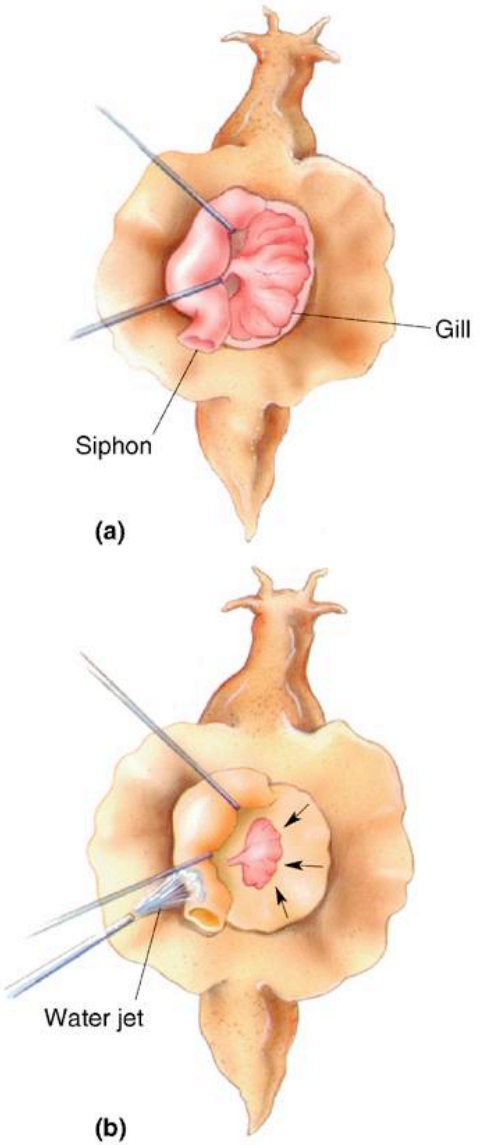
- In Hebbian plasticity, an excitatory synapse should be potentiated if it contributes to a postysynaptic action potential (AP)
- The AP would necessarily occur after the EPSP, because of the time needed for conduction down the dendrite, especially if the synapse is on a distal dendrite
- An EPSP on a dendrite spreads to the soma, triggers an AP, and then the AP backpropagates up the dendrite to the synapse
- The optimal delay between pre and postsynaptic activity found in STDP (see slide 22) may function to account for the delay between an EPSP and the backpropagating action potential that it “caused”

Invertebrate Models of Learning

- In work on synaptic plasticity in hippocampus and other vertebrate brain structures, it is very difficult to relate cellular changes to behavior of the animal
  - This is much easier in invertebrate systems
- Experimental advantages in using invertebrate nervous systems
  - Small nervous systems
  - Easily accessible nervous systems
  - Large neurons
    - Example: Squid giant axon
  - Identifiable neurons
  - Identifiable circuits
    - Each animal's nervous system has virtually the same circuitry
  - Simple genetics
    - C. elegans
    - Drosophila

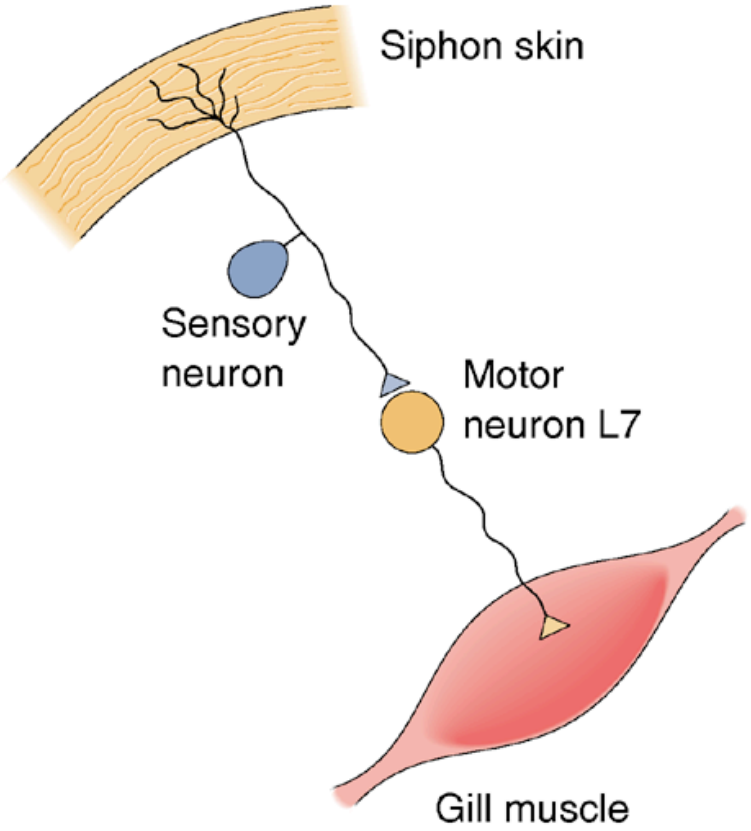
Aplysia

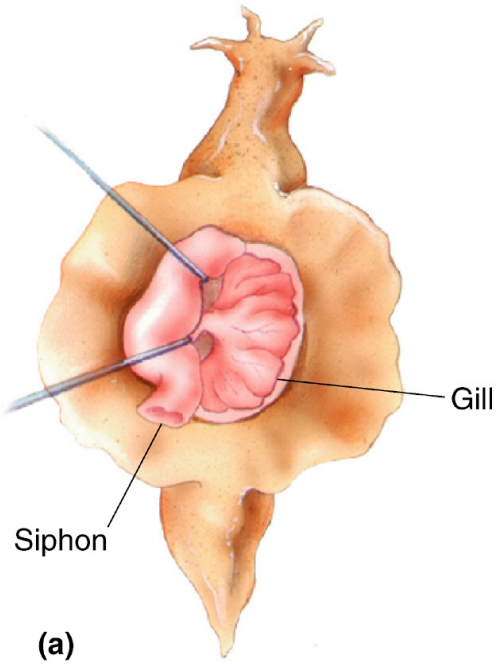
- Aplysia is a type of sea slug that has served as a model to study the cellular and molecular basis of learning and memory
- Eric Kandel shared the Nobel Prize in 2000 for his work on this topic

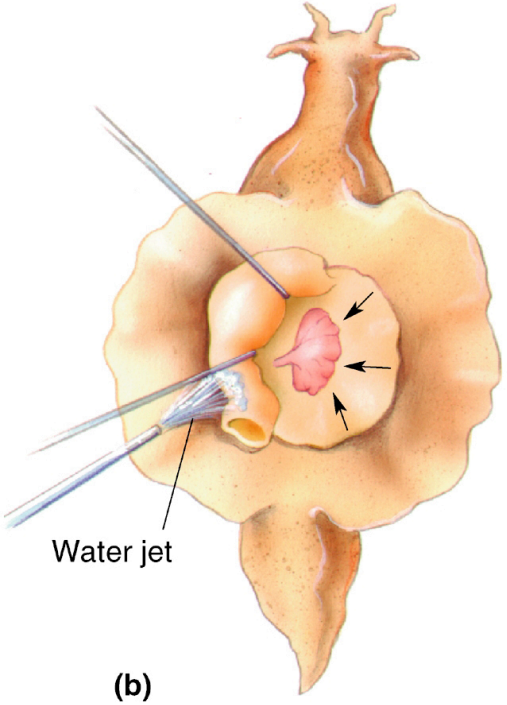


Habituation of the Gill-Withdrawal Reflex

- A mild water jet causes withdrawal of the gill
- With repeated water jets, the withdrawal of the gill habituates (becomes weaker or stops completely)

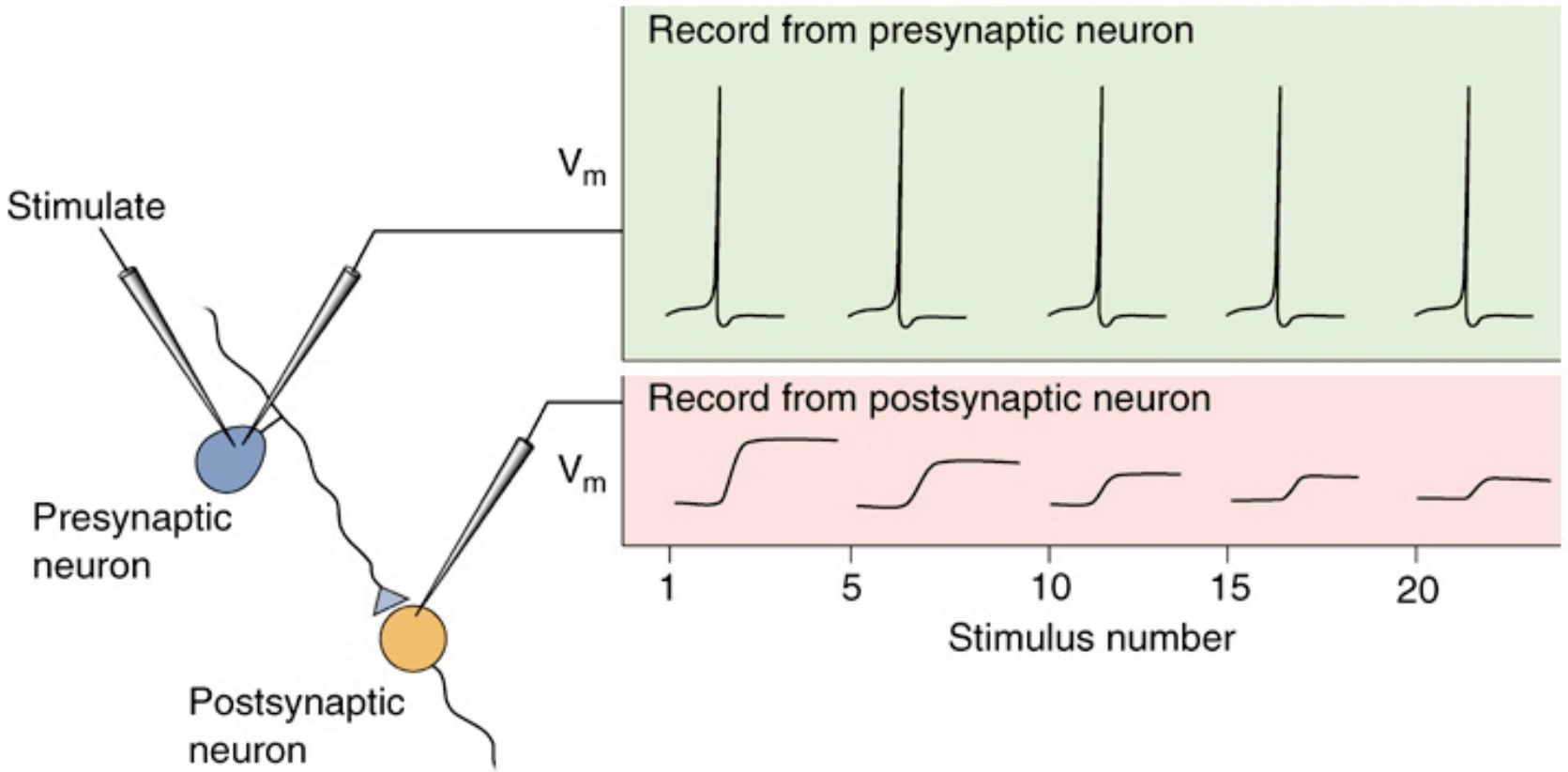






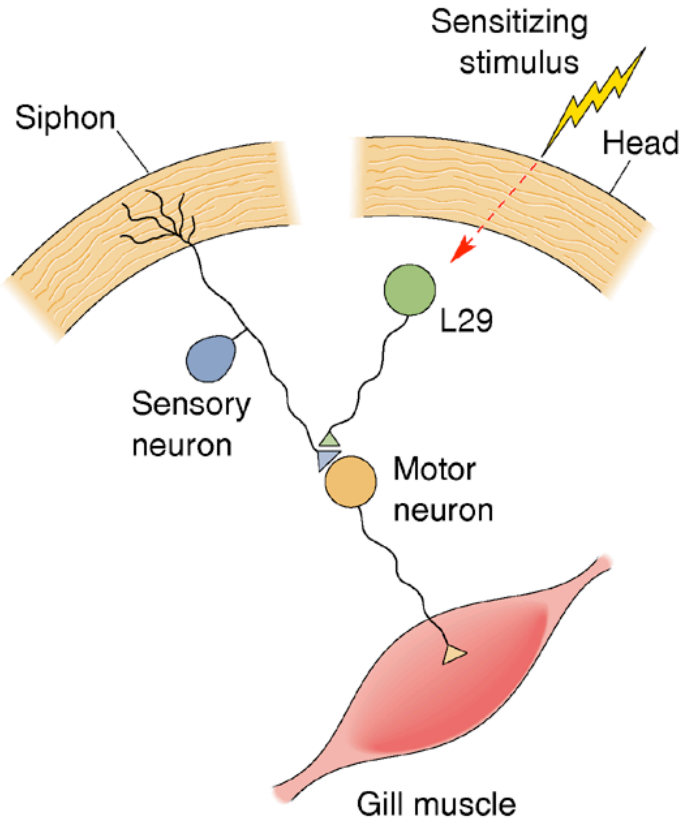
Mechanism of Habituation of the Gill-Withdrawal Reflex

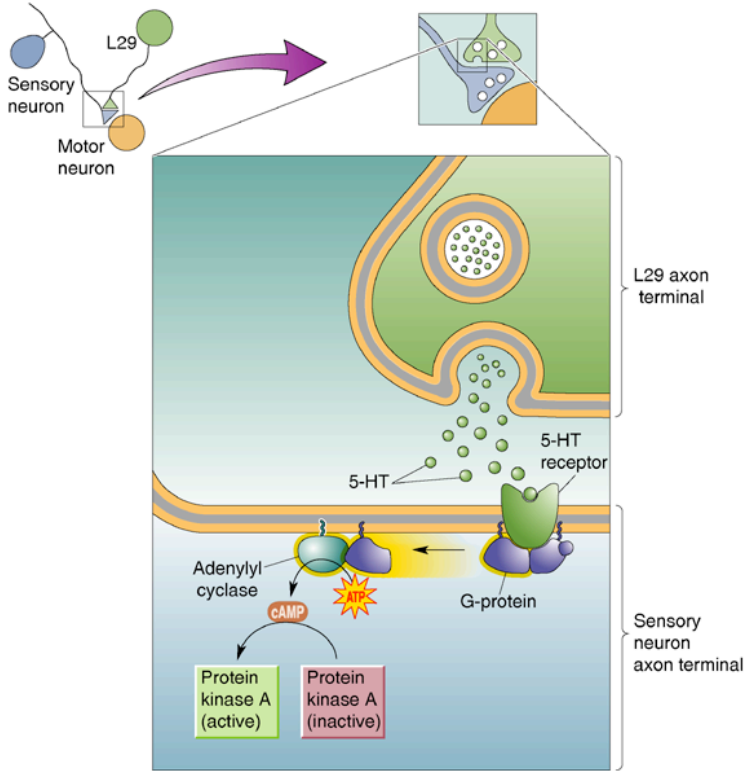
- Caused by reduction in vesicular neurotransmitter release
- Presynaptic Ca2+ channels become inactivated
- This could be understood in terms of a presynaptic terminal that signals prediction error.
  - As the action potentials become more predictable (due to their higher frequency), the vesicle release probability decreases.



Sensitization of the Gill-Withdrawal Reflex

- L29 releases serotonin (5-HT) onto synaptic terminal of sensory neuron
- Serotonin receptors shut off voltage-gated K+ channels (via a cascade of signaling events, including activation of adynylyl cyclase, increase in cAMP, activation of PKA and phosphorylation of K+ channels)
- Without these K+ channels, action potentials last longer, more Ca2+ enters the terminal, and thus more transmitter is released





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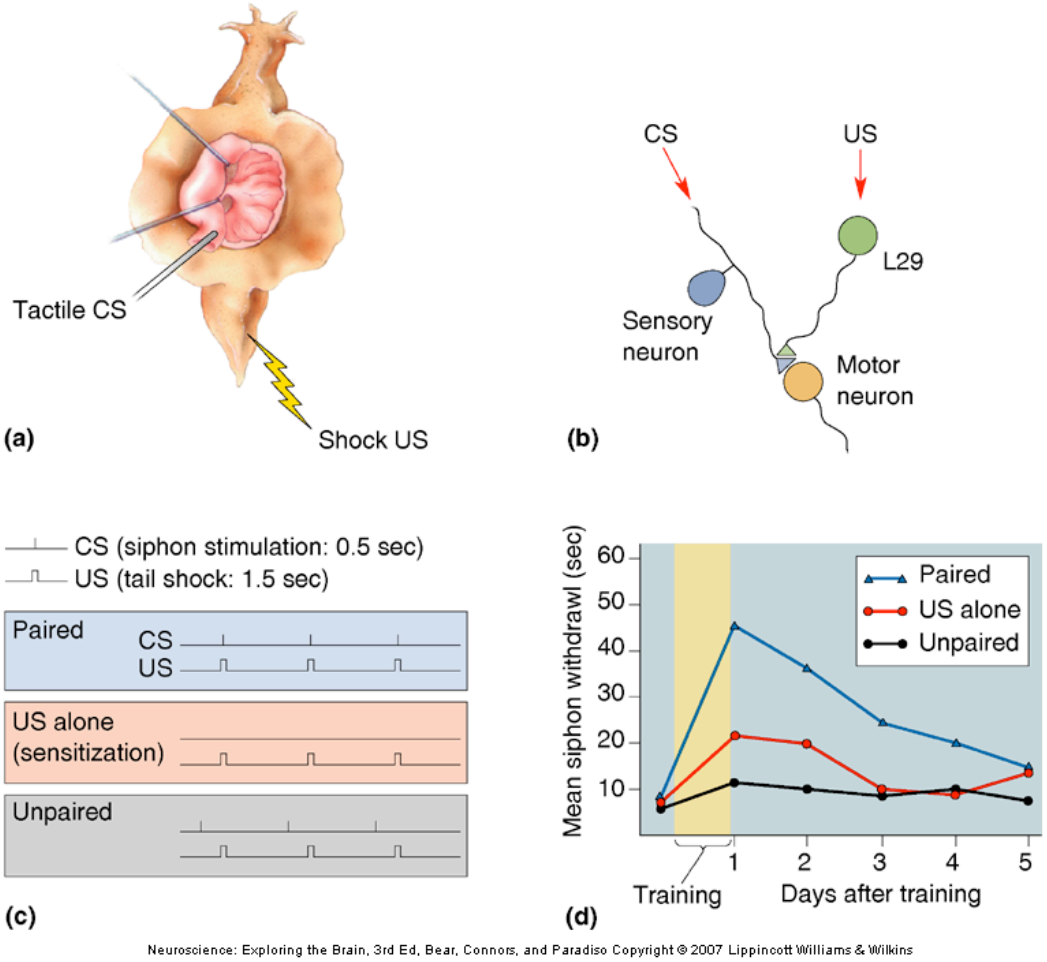
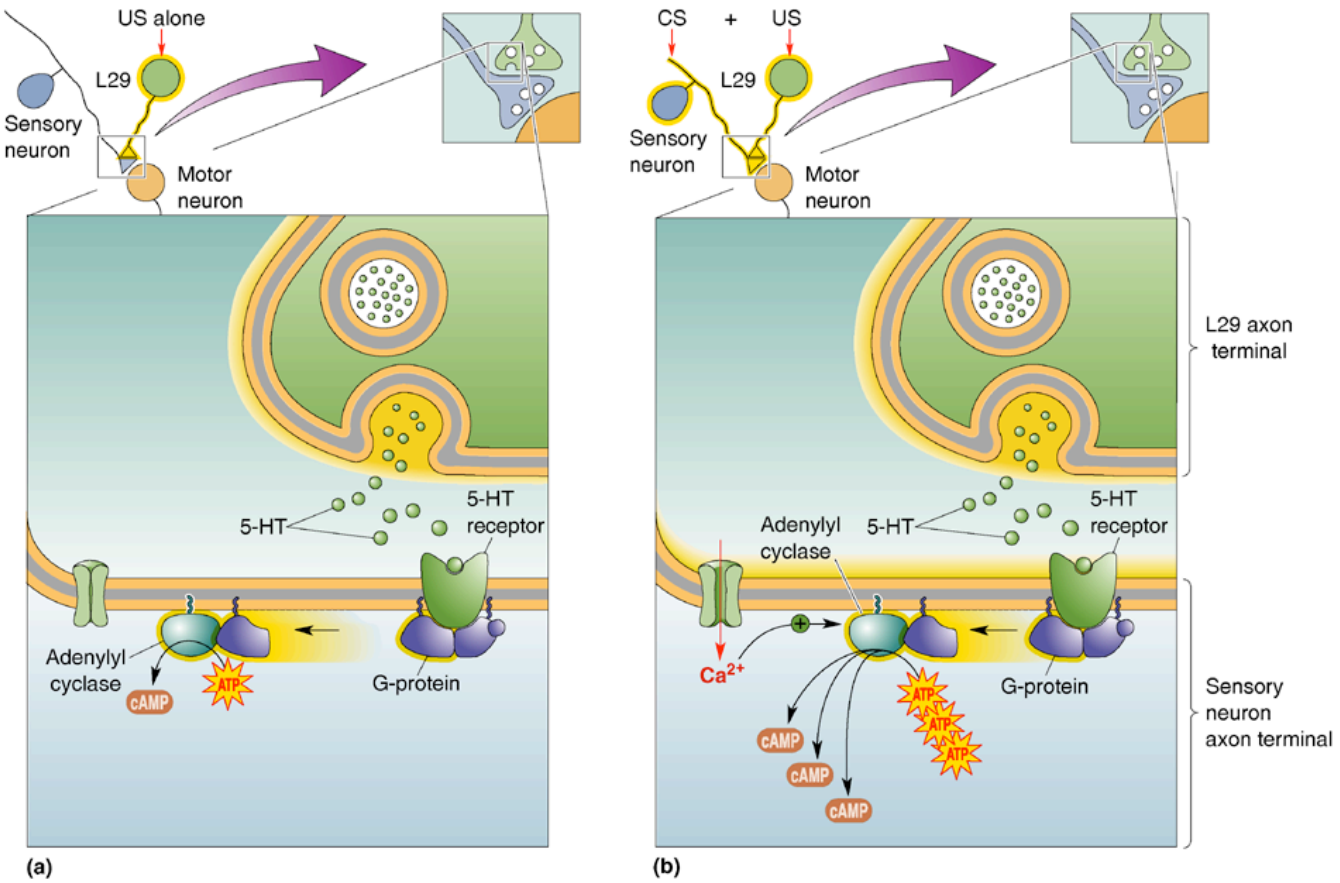
Classical (Pavlovian) conditioning in *Aplysia*

- In classical (Pavlovian) conditioning, an animal learns that a conditioned stimulus (CS) predicts an unconditioned stimulus (US)
  - The CS is a neutral sensory stimulus, and the US is a sensory event that is important to the animal (something good or bad)
  - After learning that the CS predicts the US, the animal responds to the CS in anticipation of the US
    - This is called a conditioned response (CR)
    - The CR is siphon withdrawal in this case



- The molecular basis for this form of classical conditioning in *Aplysia*
  - Serotonin represents the US
  - Ca2+ represents the CS
  - Adenylyl cyclase is the coincidence detector
    - Serotonin and Ca2+ act synergistically to increase cAMP
  - Inactivation of K+ channels is the effector, or expression mechanism (just as in sensitization)



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