Part 3, Neural Signaling

3.6. Synaptic plasticity

Synaptic plasticity

- Synaptic connections between neurons provide the basic “wiring"' of the brain's circuitry.
- Synaptic connectivity between neurons is a dynamic entity that is constantly changing in response to neural activity and other influences.
- Such changes in synaptic transmission arise from a number of forms of plasticity that vary in time scale from milliseconds to years.
- **Short-term synaptic plasticity**:
  - Most short-term forms of synaptic plasticity affect the amount of neurotransmitter released from presynaptic terminals in response to a presynaptic action potential.
  - Several forms of short-term synaptic plasticity--including facilitation, augmentation, and potentiation--enhance neurotransmitter release and are caused by persistent actions of calcium ions within the presynaptic terminal.
  - Another form of short-term plasticity, synaptic depression, decreases the amount of neurotransmitter released and appears to be due to an activity-dependent depletion of synaptic vesicles that are ready to undergo exocytosis.

Synaptic plasticity

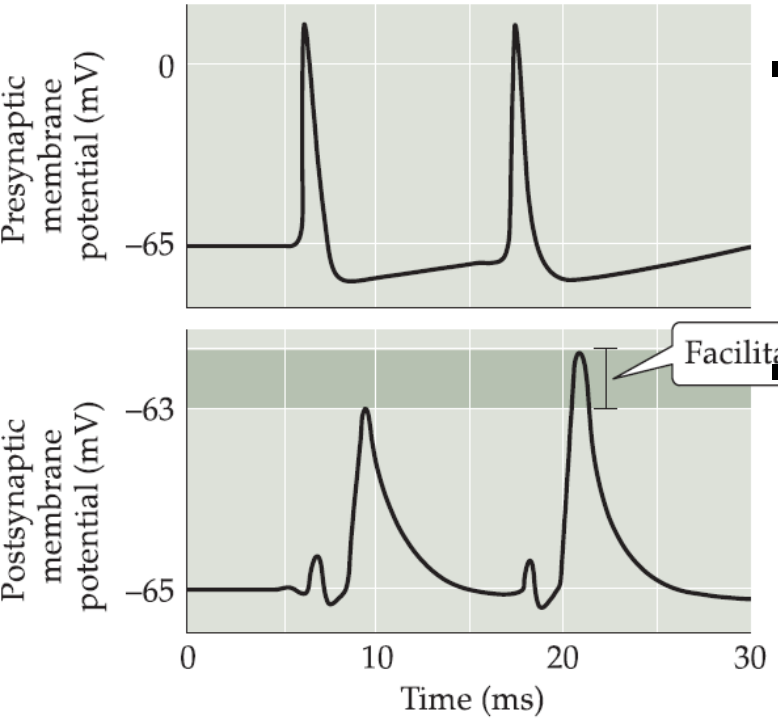
- **Long-term synaptic plasticity**:
  - Long-term forms of synaptic plasticity alter synaptic transmission over time scales of 30 minutes or longer.
  - Examples of such long-lasting plasticity include **long-term potentiation** and **long-term depression**.
  - These long-lasting forms of synaptic plasticity arise from molecular mechanisms that vary over time:
    - The initial changes in synaptic transmission arise from posttranslational modifications of existing proteins, most notably changes in the trafficking of glutamate receptors.
    - The later phases of synaptic modification result from changes in gene expression.
      - These changes in gene expression produce enduring changes in synaptic transmission, including growth of synapses, that can yield essentially permanent modifications of brain function.

Short-term synaptic plasticity

- Chemical synapses are capable of undergoing plastic changes that either strengthen or weaken synaptic transmission.
- The short-term forms of plasticity--those lasting for a few minutes or less--are readily observed during repeated activation of any chemical synapse.
- There are several forms of short-term synaptic plasticity that differ in their time courses and their underlying mechanisms.

Synaptic facilitation

- **Synaptic facilitation** is a rapid increase in synaptic strength that occurs when two or more action potentials invade the presynaptic terminal within a few milliseconds of each other.
  - A pair of presynaptic action potentials elicits two excitatory postsynaptic potentials (EPSPs).
  - Because of facilitation, the second EPSP is larger than the first.
- Many lines of evidence indicate that facilitation is the result of prolonged elevation of presynaptic calcium levels following synaptic activity.



- Although the entry of Ca^{2+} into the presynaptic terminal occurs within a millisecond or two after an action potential invades, the mechanisms that return Ca^{2+} to resting levels are much slower.
- Thus, when action potentials arrive close together in time, calcium builds up within the terminal and allows more neurotransmitters to be released by a subsequent presynaptic action potential.

Synaptic depression

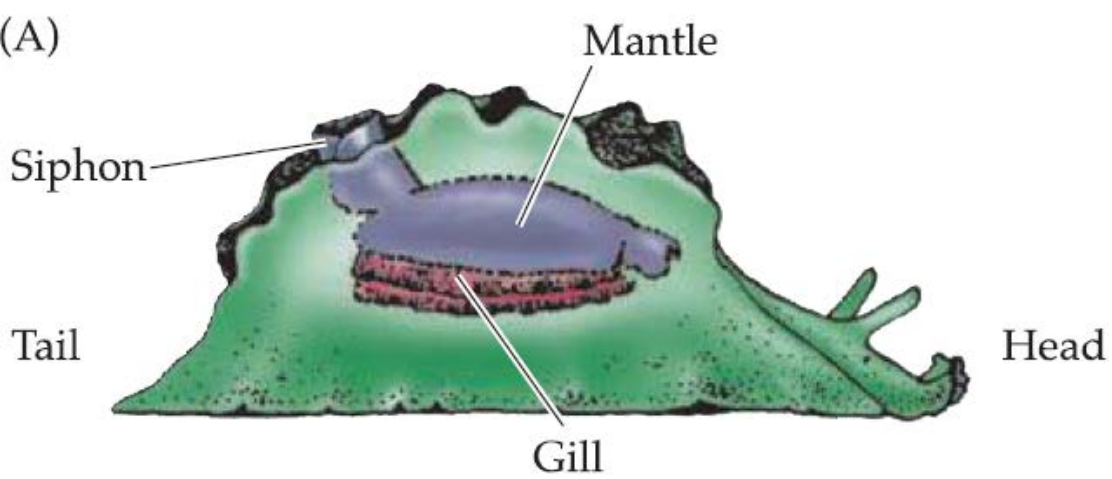
- Opposing facilitation is **synaptic depression**, which causes neurotransmitter release to decline during sustained synaptic activity.
- An important clue to the cause of synaptic depression comes from observations that depression depends on the amount of neurotransmitter that has been released.
- For example, lowering the external Ca^{2+} concentration, to reduce the number of quanta released by each presynaptic action potential, causes the rate of depression to be slowed.
- Depression is caused by progressive depletion of a pool of synaptic vesicles that are available for release: when rates of release are high, these vesicles deplete rapidly and cause a lot of depression; depletion slows as the rate of release is reduced, yielding less depression.

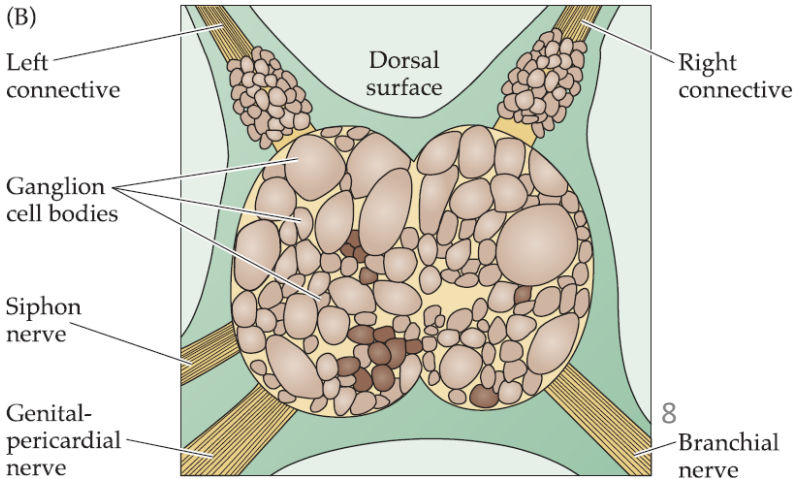
Synaptic potentiation and augmentation

- Other forms of synaptic plasticity, such as **synaptic potentiation** and **augmentation**, also are elicited by repeated synaptic activity and serve to increase the amount of transmitter released from presynaptic terminals.
- Both augmentation and potentiation enhance the ability of incoming calcium ions to trigger fusion of synaptic vesicles with the plasma membrane, but work over different time scales.
  - Augmentation rises and falls over a few seconds.
  - Potentiation acts over a time scale of tens of seconds to minutes.
- Although both augmentation and potentiation are thought to arise from prolonged elevation of presynaptic calcium levels during synaptic activity, the mechanisms responsible for these forms of plasticity are poorly understood.
- During repetitive synaptic activity, these forms of short-term plasticity can interact to cause synaptic transmission to change in complex ways.

Synaptic plasticity in *Aplysia*

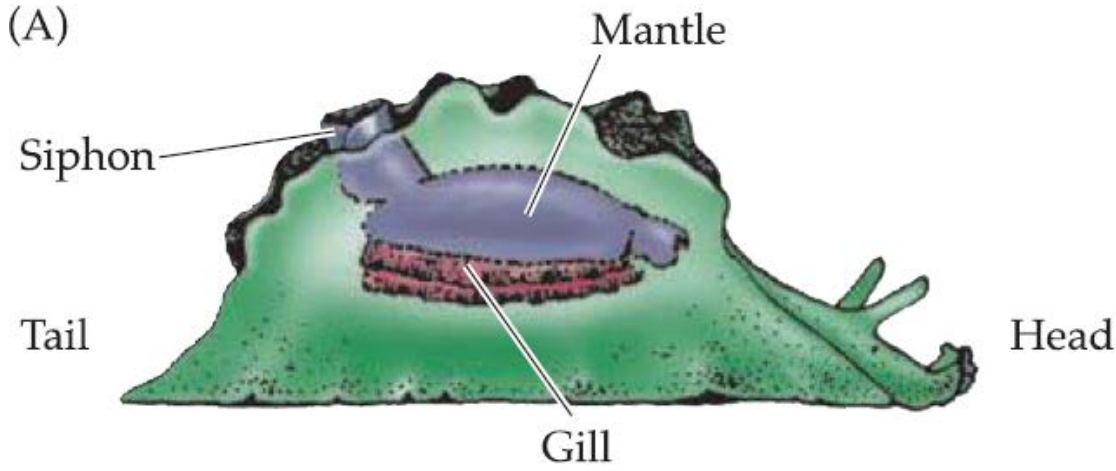
- **Eric Kandel** (2000 Nobel Prize) and his colleagues at Columbia University have used the marine mollusk *Aplysia californica* to study synaptic plasticity.
  - This sea slug has only a few tens of thousands of neurons, many of which are quite large (up to 1 mm in diameter) and in stereotyped locations within the ganglia that make up the animal's nervous system.
  - These attributes make it practical to monitor the electrical activity of specific, identifiable nerve cells, and thus to define the synaptic circuits involved in mediating the limited behavioral repertoire of *Aplysia*.
  - *Aplysia* exhibit several elementary forms of behavioral plasticity.

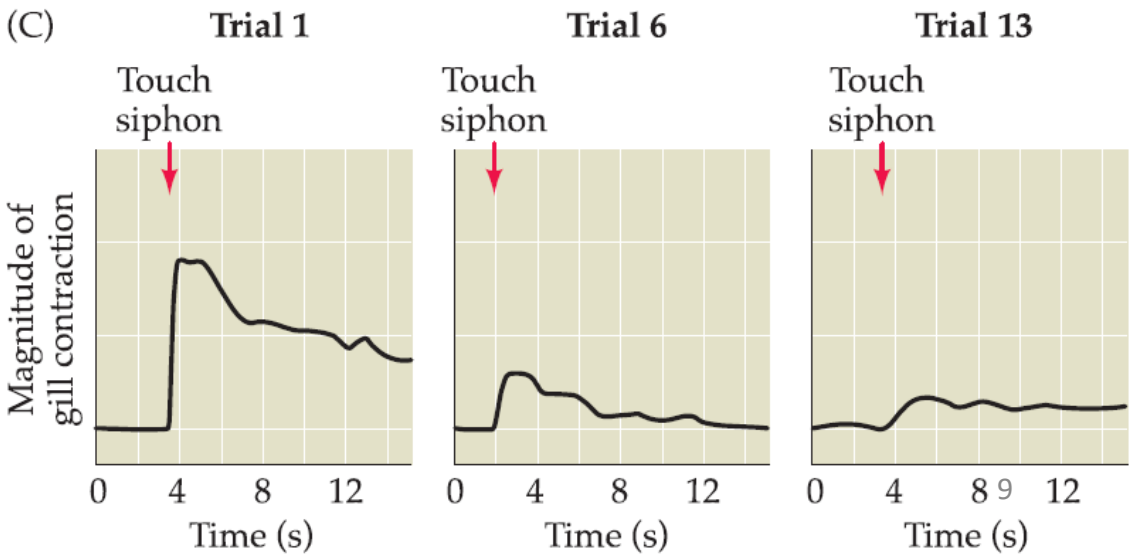




Habituation

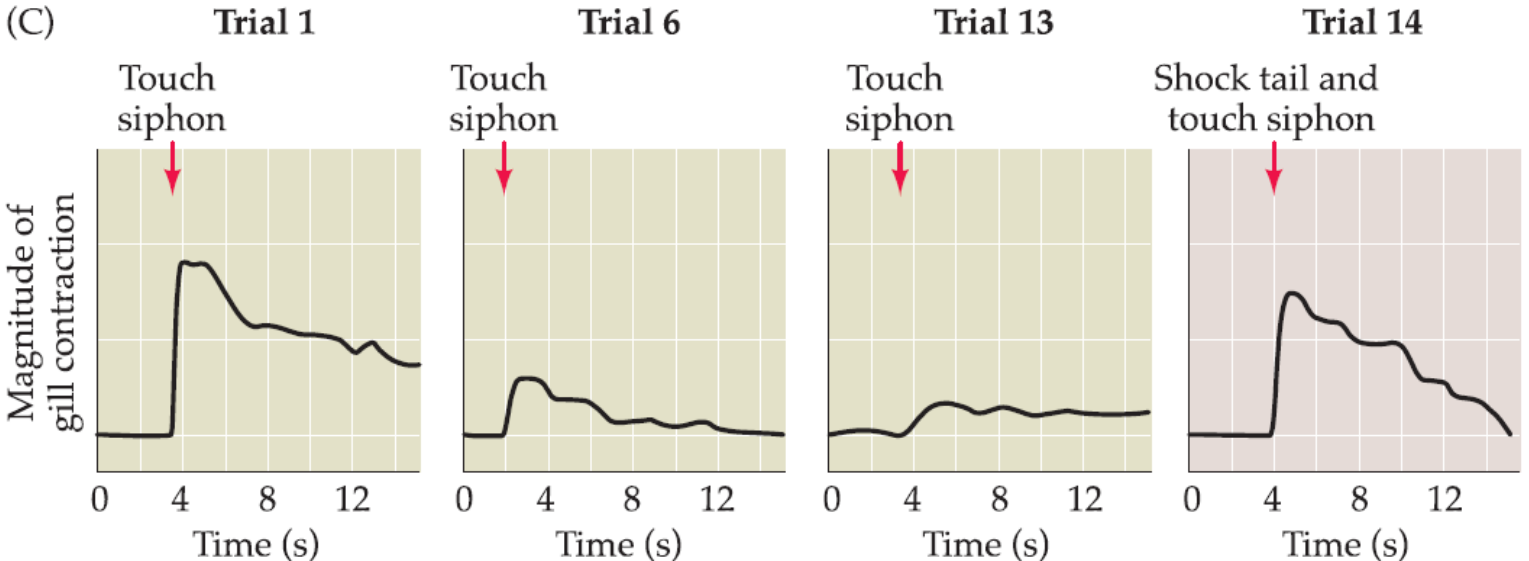
- **Habituation** is a process that causes the animal to become less responsive to repeated occurrences of a stimulus.
  - Habituation is found in many other species, including humans.
  - Habituation in humans?
  - A light touch to the siphon of an *Aplysia* results in withdrawal of the animal's gill, but habituation causes the gill withdrawal to become weaker during repeated stimulation of the siphon.





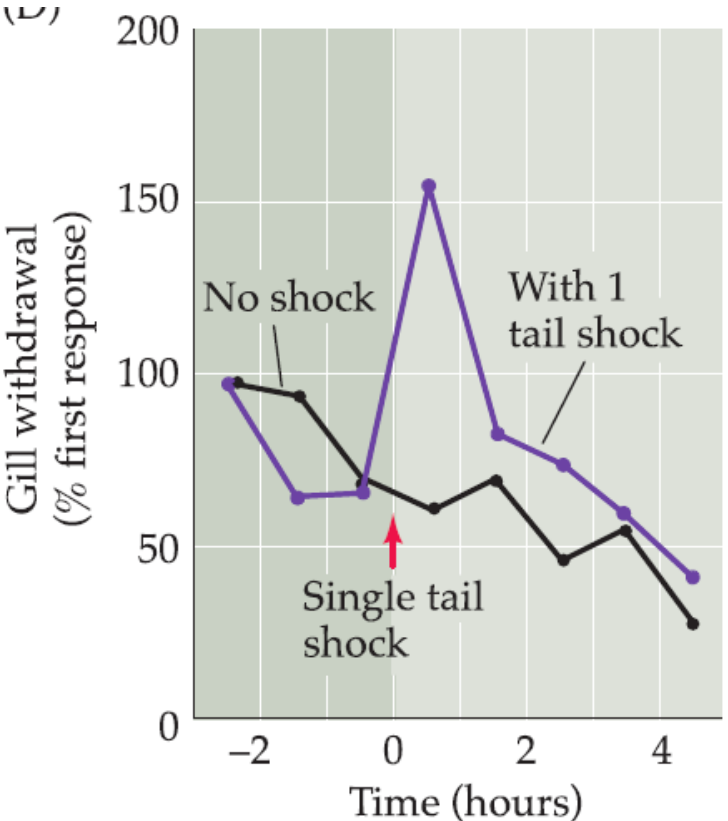
Sensitization

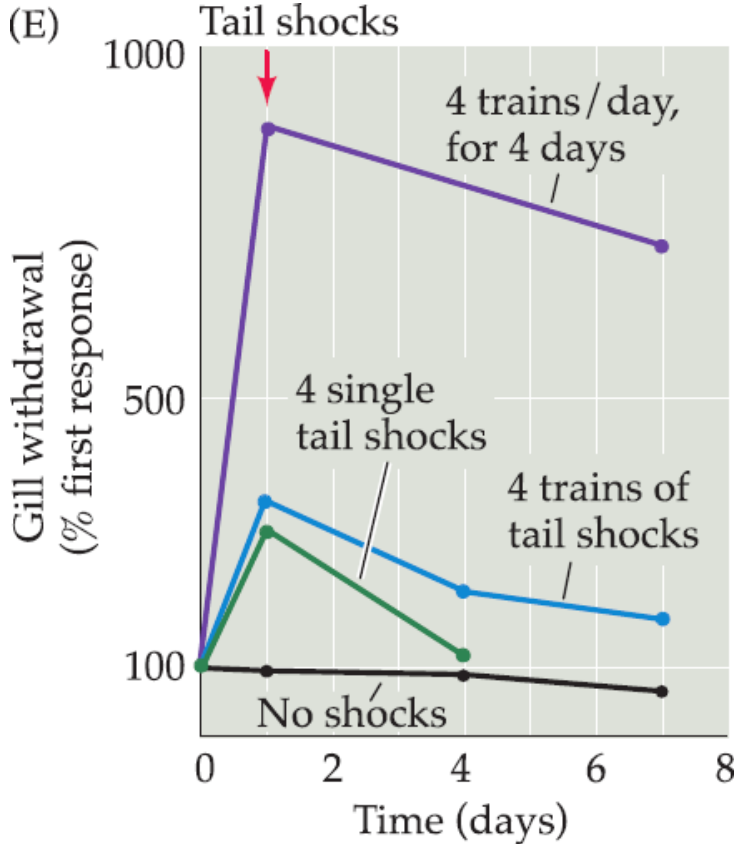
- The gill-withdrawal response of *Aplysia* exhibits another form of plasticity called **sensitization**.
  - Sensitization is a process that allows an animal to generalize an aversive response elicited by a noxious stimulus to a variety of other, non-noxious stimuli.
  - In *Aplysia* that have habituated to siphon touching, sensitization of gill withdrawal is elicited by pairing a strong electrical stimulus to the animal's tail with another light touch of the siphon.
  - This pairing causes the siphon stimulus to again elicit a strong withdrawal of the gill because the noxious stimulus to the tail sensitizes the gill-withdrawal reflex to light touch.



Sensitization

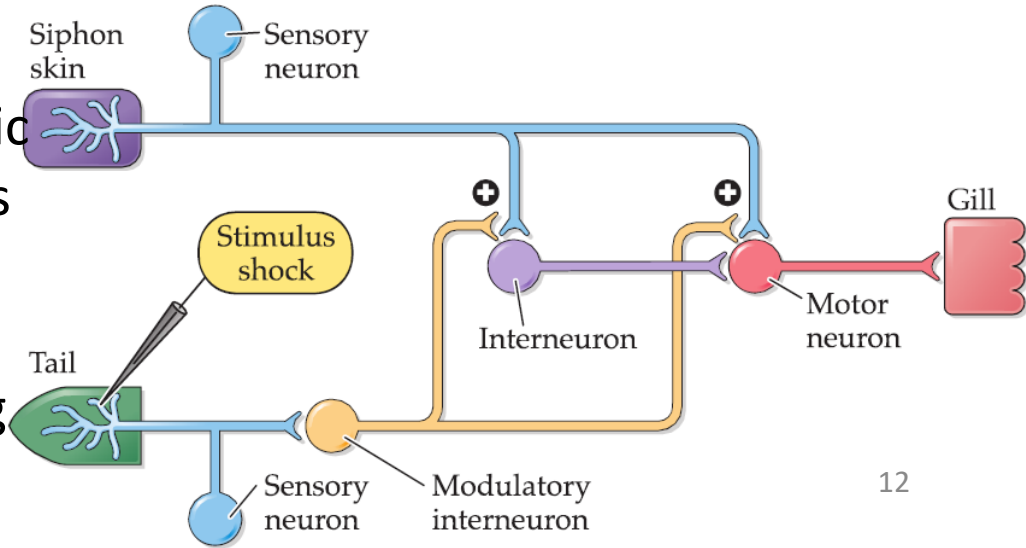
- Even after a single stimulus to the tail, the gill-withdrawal reflex remains enhanced for at least an hour, which can be viewed as a simple form of short-term memory.
- With repeated pairing of tail and siphon stimuli, this behavior can be altered for days or weeks, also demonstrating a simple form of long-term memory.





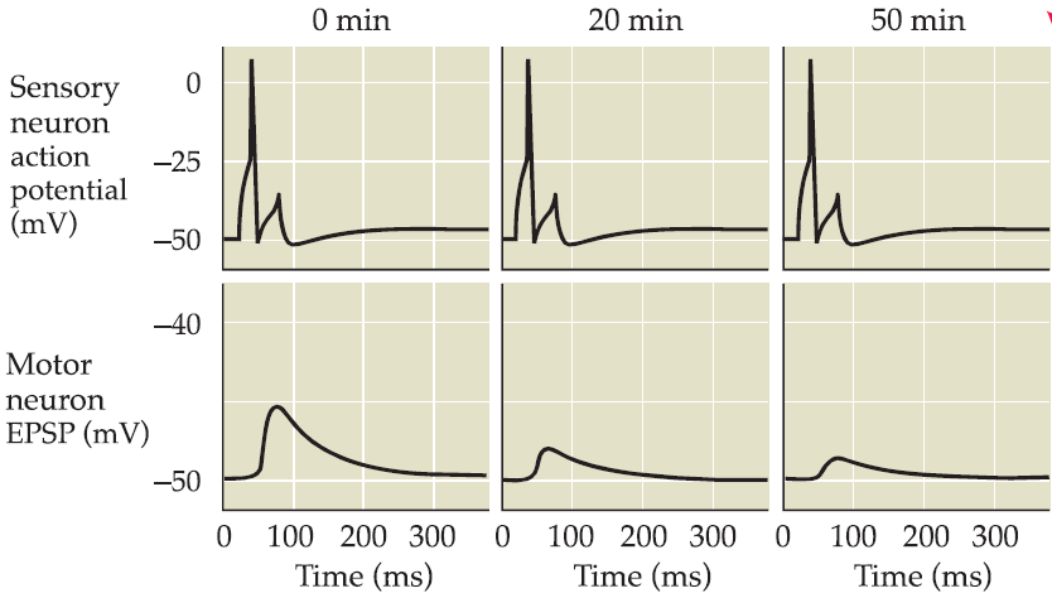
Synaptic mechanisms in *Aplysia*

- The small number of neurons in the *Aplysia* nervous system makes it possible to define the synaptic circuits involved in gill withdrawal and to monitor the activity of individual neurons in these circuits:
  - Mechanosensory neurons that innervate the siphon.
  - Motor neurons that innervate muscles in the gill.
  - Interneurons that receive inputs from a variety of sensory neurons.
- Touching the siphon activates the mechanosensory neurons, which form excitatory synapses that release glutamate onto both the interneurons and the motor neurons.
- The interneurons form excitatory synapses on motor neurons.
- When the motor neurons are activated by the summed synaptic excitation of the sensory neurons and interneurons, they release acetylcholine that excites the muscle cells of the gill, producing gill withdrawal.



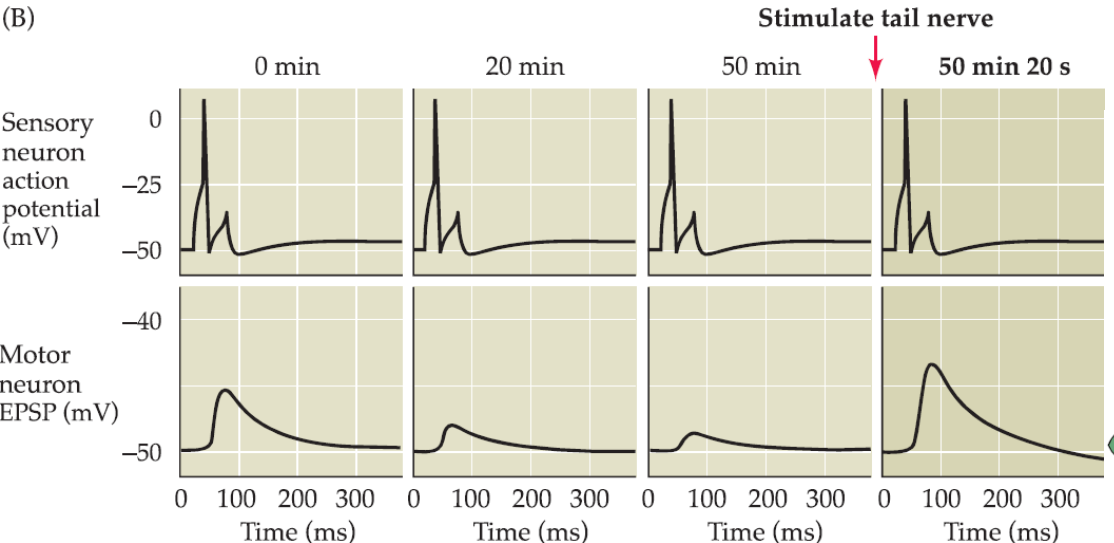
Synaptic mechanisms underlying short-term sensitization

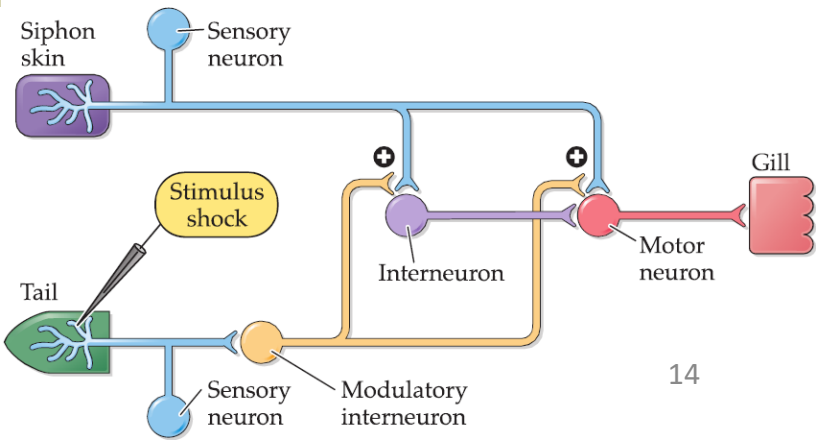
- During habituation, transmission at the glutamatergic synapse between the sensory and motor neurons is depressed.
- This synaptic depression is thought to be responsible for the decreasing ability of siphon stimuli to evoke gill contractions during habituation.
- This depression is presynaptic and is due to a reduction in the number of synaptic vesicles available for release.



Synaptic mechanisms underlying short-term sensitization

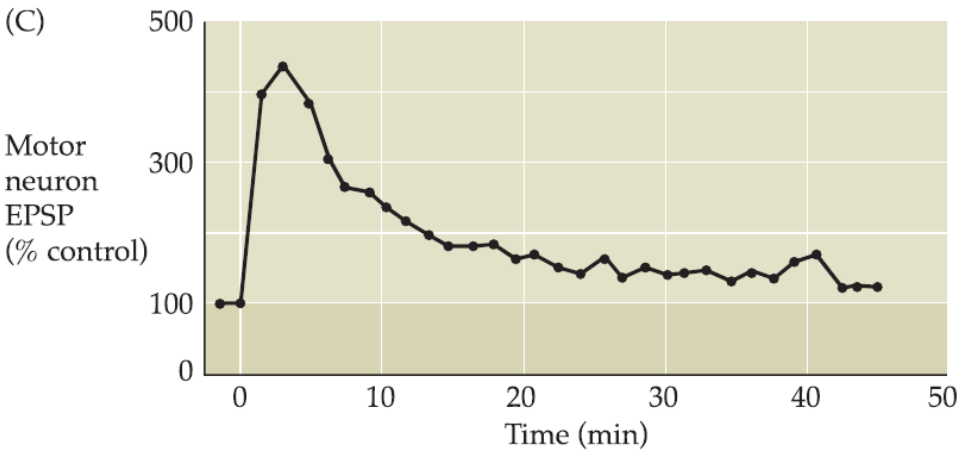
- Sensitization modifies the function of this circuit by recruiting additional neurons.
- The tail shock that evokes sensitization activates sensory neurons that innervate the tail.
- These sensory neurons in turn excite modulatory interneurons that release serotonin onto the presynaptic terminals of the sensory neurons of the siphon.
- Serotonin enhances transmitter release from the siphon sensory neuron terminals, leading to increased synaptic excitation of the motor neurons.

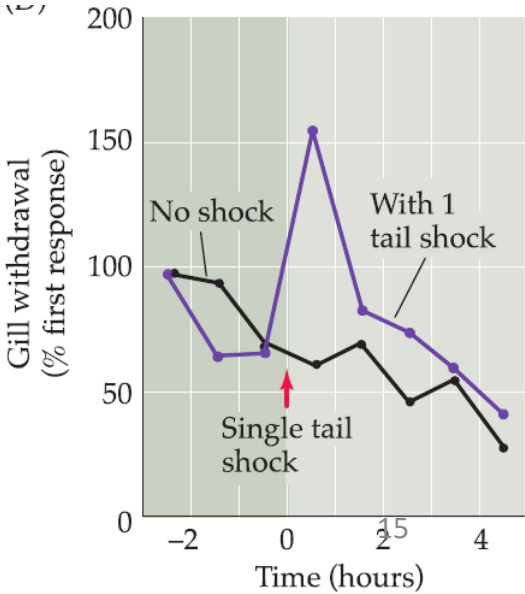




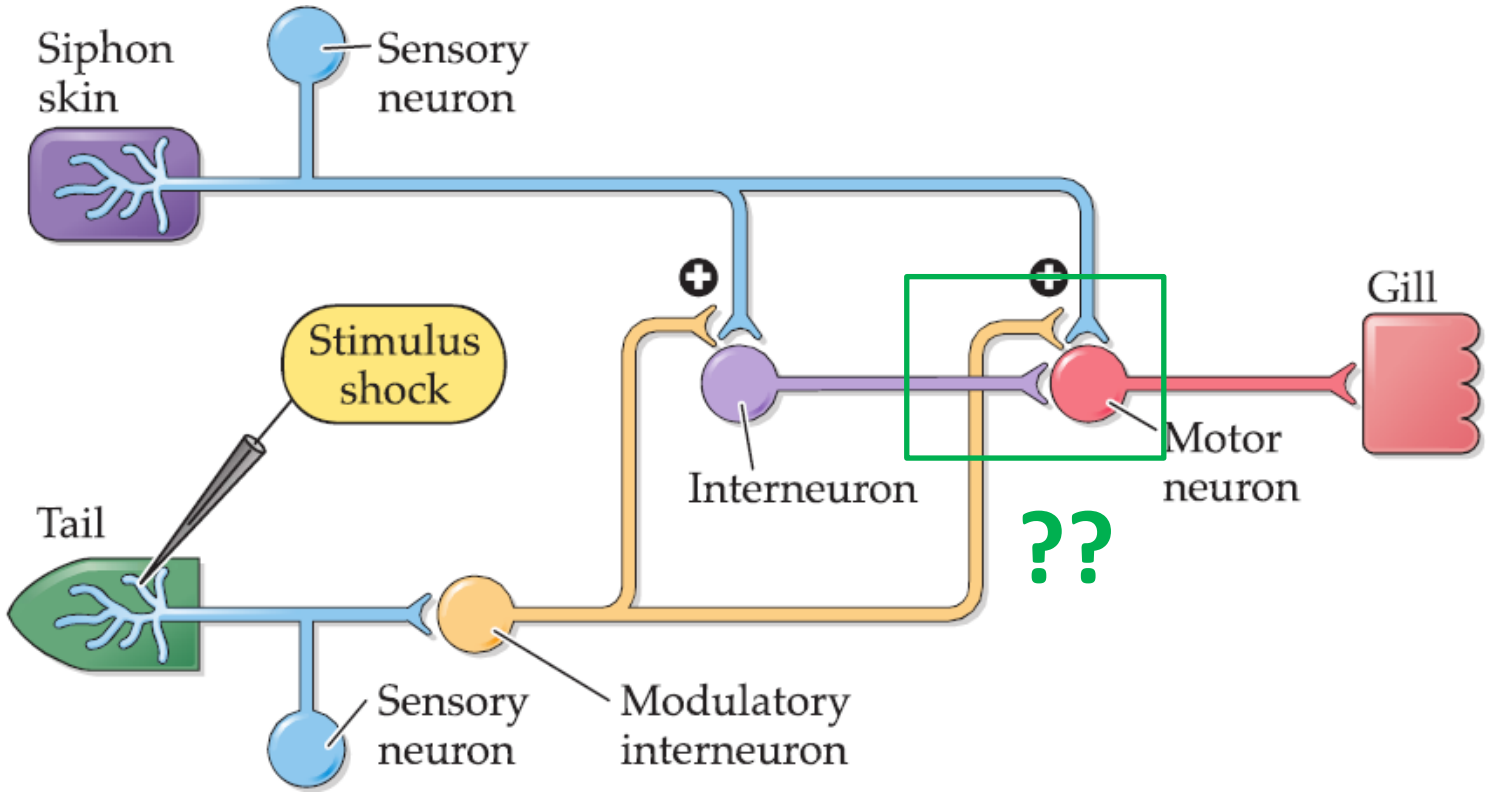
Synaptic mechanisms underlying short-term sensitization

- This modulation of the sensory neuron-motor neuron synapse lasts approximately an hour.
- This is similar to the duration of the short-term sensitization of gill withdrawal produced by applying a single stimulus to the tail.
- Thus, the short-term sensitization apparently is due to recruitment of additional synaptic elements that modulate synaptic transmission in the gill-withdrawal circuit.



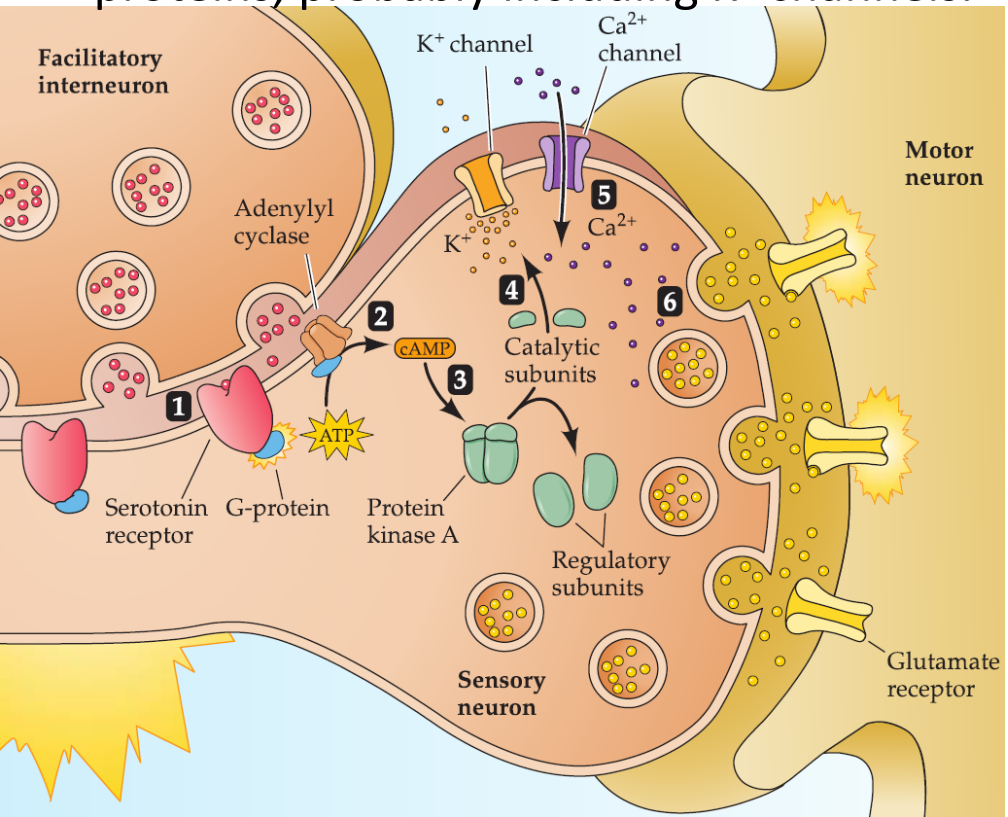


Synaptic mechanisms underlying short-term sensitization



Mechanism of presynaptic enhancement underlying short-term sensitization

1. Serotonin released by the facilitatory interneurons binds to G-protein-coupled receptors on the presynaptic terminals of the siphon sensory neurons.
2. This stimulates production of the second messenger, cAMP.
3. Cyclic AMP binds to the regulatory subunits of protein kinase A.
4. This liberate catalytic subunits of PKA that are then able to phosphorylate several proteins, probably including K^+ channels.



- The net effect of the action of PKA is to reduce the probability that the K^+ channels open during a presynaptic action potential.

5. This effect prolongs the presynaptic action potential, thereby opening more presynaptic Ca^{2+} channels.
6. The enhanced influx of Ca^{2+} into the presynaptic terminals increases the amount of transmitter released onto motor neurons during a sensory neuron action potential.

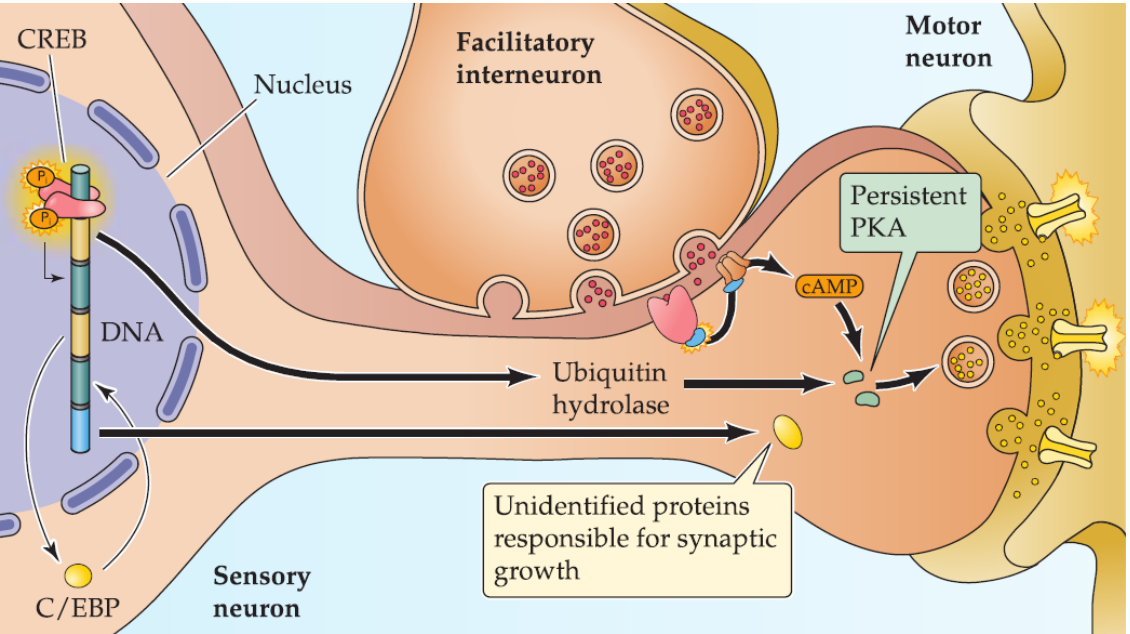
Mechanism of presynaptic enhancement underlying short-term sensitization

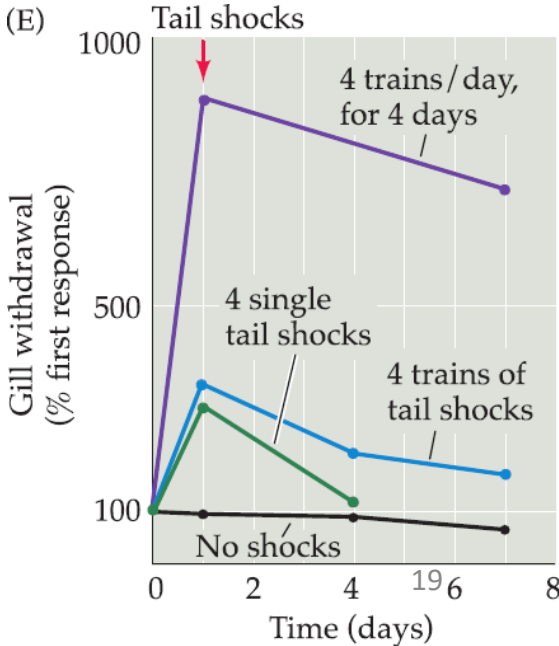
- In summary, a signal transduction cascade that involves neurotransmitters, second messengers, protein kinases, and ion channels mediates short-term sensitization of gill withdrawal.

- This cascade ultimately enhances synaptic transmission between the sensory and motor neurons within the gill-withdrawal circuit.

Mechanism of presynaptic enhancement underlying long-term sensitization

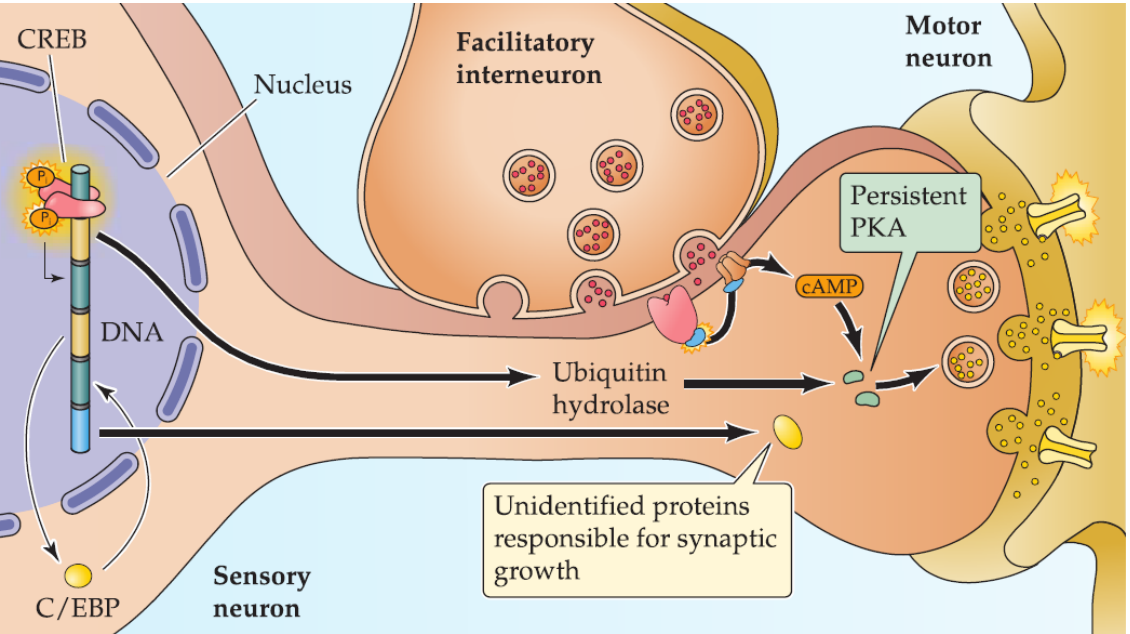
- The same serotonin-induced enhancement of glutamate release that mediates short-term sensitization is also thought to underlie long-term sensitization.
- The prolonged duration of this form of plasticity is evidently due to changes in gene expression and thus protein synthesis.
- With repeated training (i.e., additional tail shocks), the serotonin-activated PKA involved in short-term sensitization now also phosphorylates--and thereby activates--the transcriptional activator CREB.





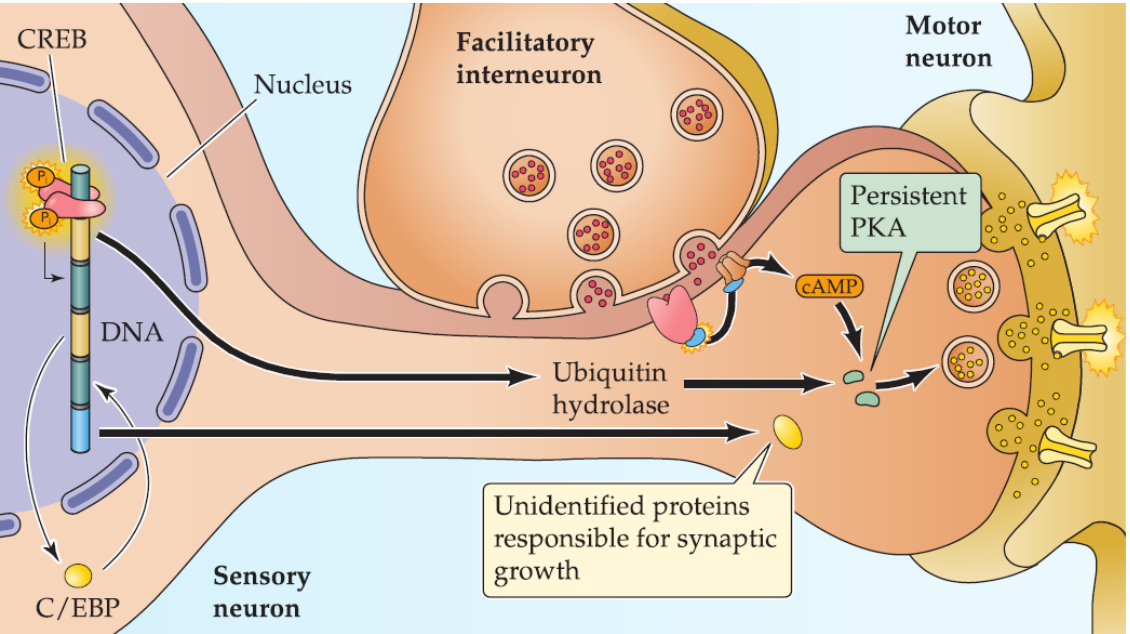
Mechanism of presynaptic enhancement underlying long-term sensitization

1. CREB stimulates the synthesis of an enzyme, ubiquitin hydroxylase, that stimulates degradation of the regulatory subunit of PKA.
   - This causes a persistent increase in the amount of free catalytic subunit, meaning that some PKA is persistently active and no longer requires serotonin to be activated.
2. CREB also stimulates another transcriptional activator protein called C/EBP.
   - C/EBP stimulates transcription of other, unknown genes that cause addition of synaptic terminals, yielding a long-term increase in the number of synapses between the sensory and the motor neurons.



Mechanism of presynaptic enhancement underlying long-term sensitization

- Another protein involved in the long-term synaptic facilitation is a cytoplasmic polyadenylation element binding protein, CPEB.
  - CPEB activates mRNAs and may be important for local control of protein synthesis.
  - CPEB has self-sustaining properties like those of prion proteins, which could allow CPEB to remain active in perpetuity and thereby mediate permanent changes in synaptic structure.



Synaptic plasticity in invertebrates

- These studies of *Aplysia* and related work on other invertebrates, such as the fruit fly, have led to several generalizations about synaptic plasticity:

1. Synaptic plasticity clearly can lead to changes in circuit function and, ultimately, to behavioral plasticity.
2. These plastic changes in synaptic function can be either short-term effects that rely on posttranslational modification of existing synaptic proteins, or they can be long-term changes that require changes in gene expression, new protein synthesis, and growth of new synapses (or the elimination of existing ones).

Long-term synaptic plasticity in mammals

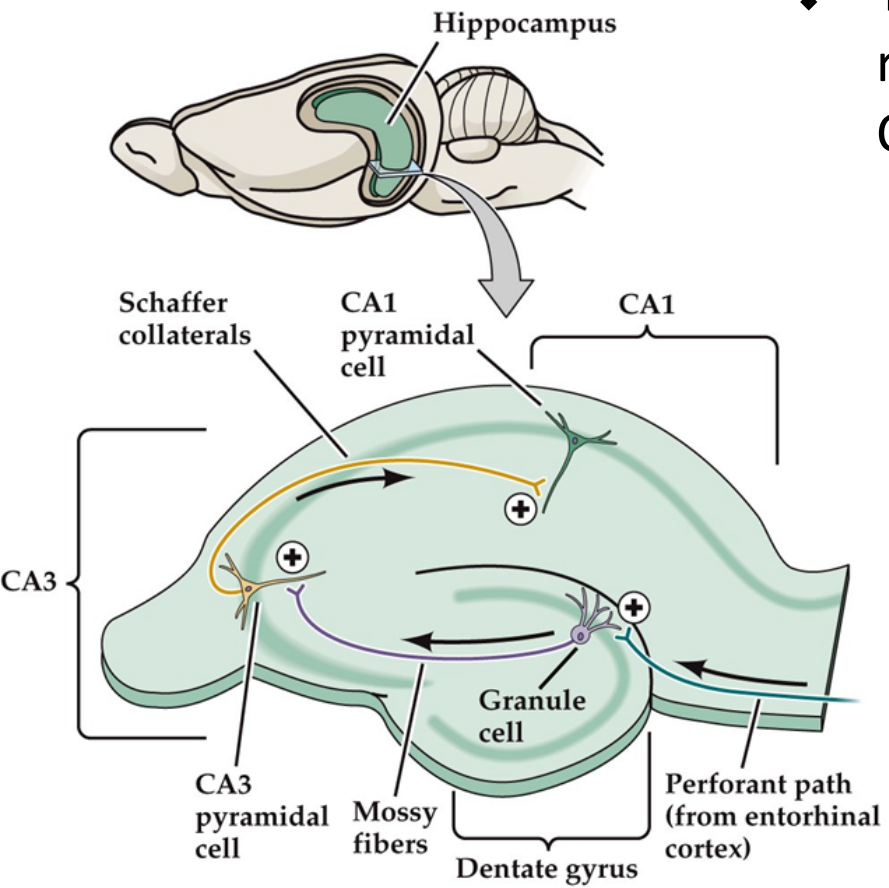
- Long-term synaptic plasticity has also been identified within the mammalian brain:
  1. Some patterns of synaptic activity produce a long-lasting increase in synaptic strength known as **long-term potentiation** (**LTP**).
  2. Other patterns of activity produce a long-lasting decrease in synaptic strength, known as **long-term depression** (**LTD**).
- LTP and LTD are produced by different histories of activity and are mediated by different complements of intracellular signal transduction pathways in the nerve cells involved.

Long-term potentiation at a hippocampal synapse

- Long-term synaptic plasticity has been most thoroughly studied at excitatory synapses in the mammalian hippocampus.
- The hippocampus is especially important in the formation and/or retrieval of some forms of memory.
  - In humans, functional imaging shows that the hippocampus is activated during certain kinds of memory tasks and that damage to this brain region results in an inability to form certain types of new memories.
  - In rodents, certain hippocampal neurons fire action potentials only when an animal is in certain locations.
    - Such “place cells” (John O'Keefe, 2014 Nobel Prize) appear to encode spatial memories, an interpretation supported by the fact that hippocampal damage prevents rats from developing proficiency in spatial learning tasks.
- Work on LTP began in the late 1960s, when Terje Lomo and Timothy Bliss, working in the laboratory of Per Andersen in Oslo, Norway, discovered that a few seconds of high-frequency electrical stimulation can enhance synaptic transmission in the rabbit hippocampus for days or even weeks.
- More recently, however, progress in understanding the mechanism of LTP has relied heavily on in vitro studies of slices of living hippocampus.

Trisynaptic circuit of hippocampus

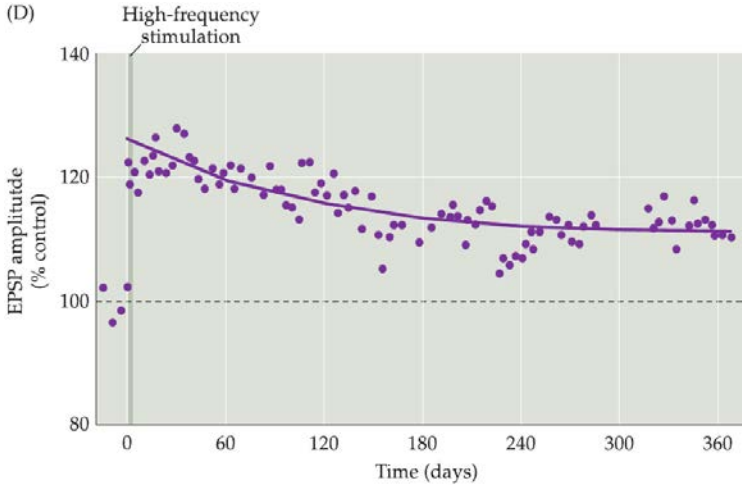
- The arrangement of neurons allows the hippocampus to be sectioned such that most of the relevant circuitry is left intact.
- In such preparations, the cell bodies of the pyramidal neurons lie in a single densely packed layer that is readily apparent.

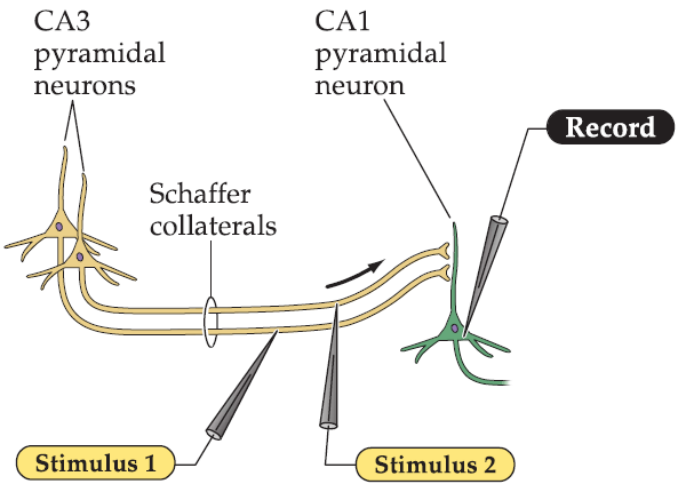


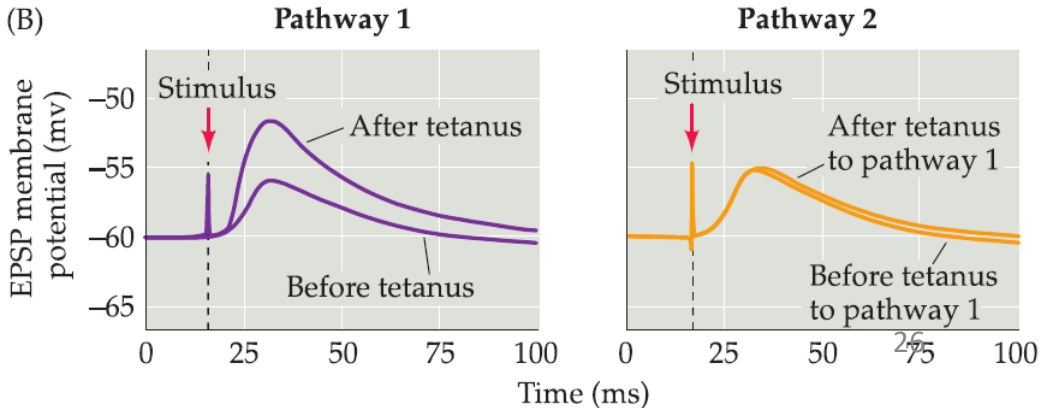
- This layer is divided into several distinct regions, the major ones being CA1 and CA3.
  - "CA" refers to *cornu Ammonis*, Latin for Ammon's horn--the ram's horn that resembles the shape of the hippocampus.
  - The dendrites of pyramidal cells in the CA1 region form a thick band (the stratum radiatum), where they receive synapses from Schaffer collaterals, the axons of pyramidal cells in the CA3 region.

Long-term potentiation of Schaffer collateral-CA1 synapses

- Much of the work on LTP has focused on the synaptic connections between the Schaffer collaterals and CA1 pyramidal cells.
- Electrical stimulation of Schaffer collaterals generates excitatory postsynaptic potentials (EPSPs) in the postsynaptic CA1 cells .
  - If the Schaffer collaterals are stimulated only two or three times per minute, the size of the evoked EPSP in the CA1 neurons remains constant.
  - However, a brief, high-frequency train of stimuli to the same axons causes LTP, which is evident as a long-lasting increase in EPSP amplitude.
  - While the maximum duration of LTP is not known, LTP can last for more than a year in some cases.



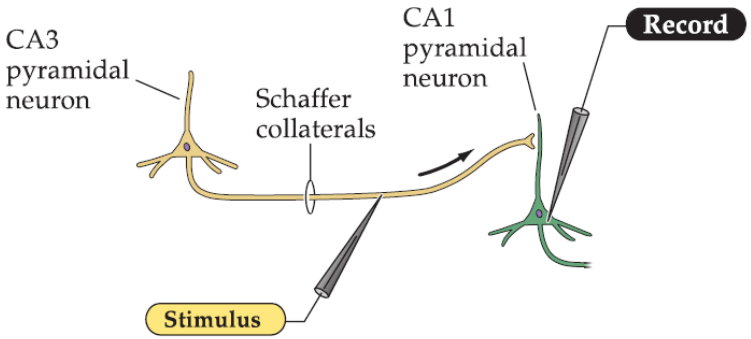


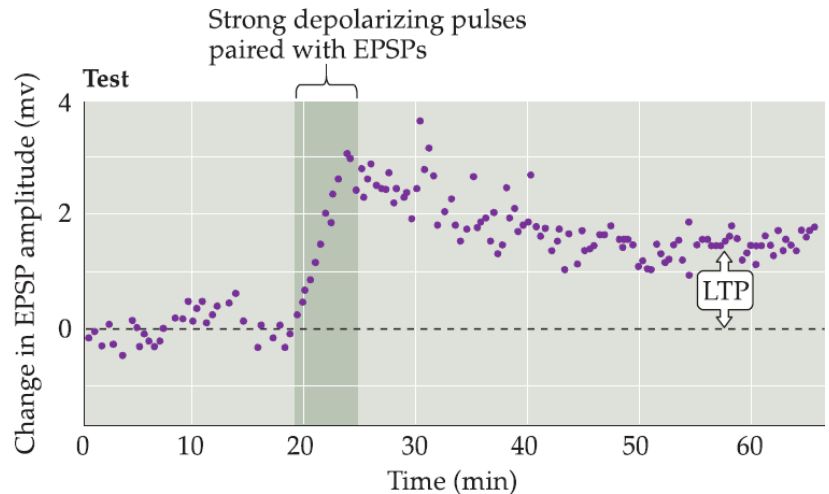


Properties of LTP in Schaffer collateral-CA1 synapses

❖ LTP of the Schaffer collateral synapse exhibits several properties that make it an attractive neural mechanism for information storage.

1. LTP requires strong activity in both presynaptic and postsynaptic neurons.

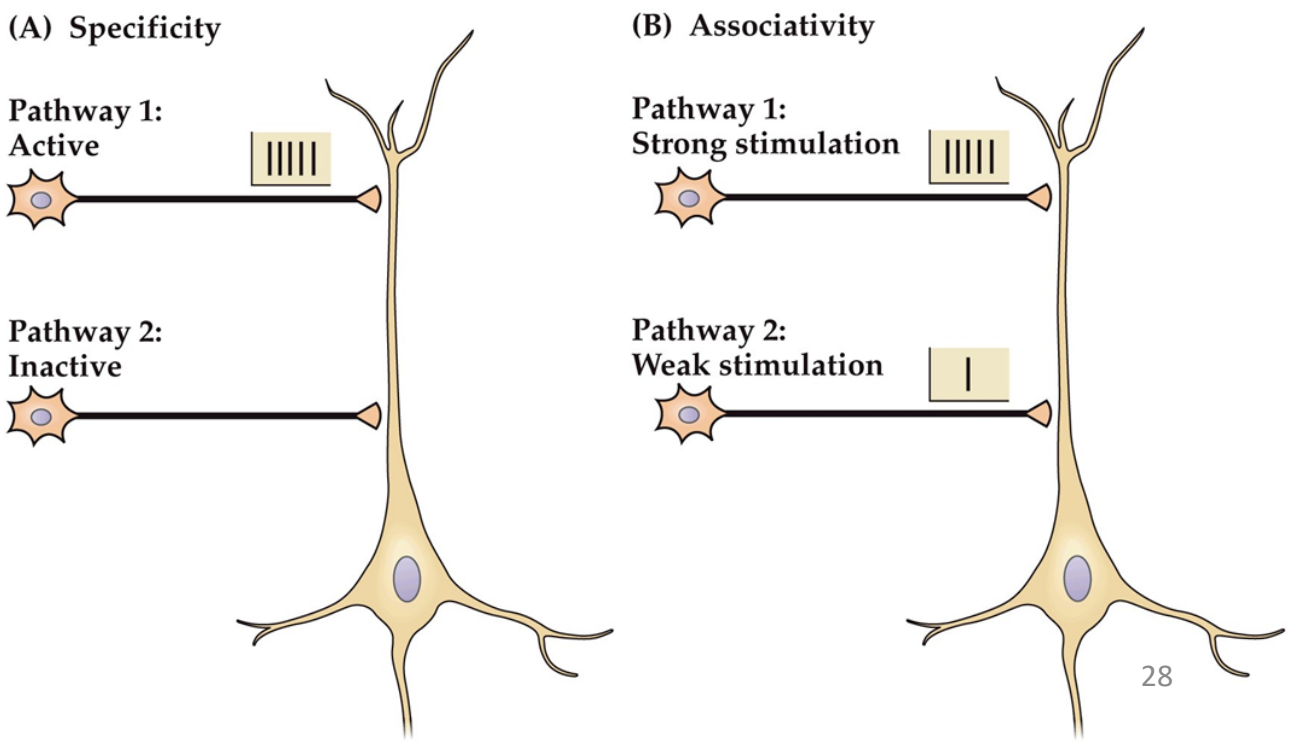




- If action potentials in a small number of presynaptic Schaffer collaterals--which evokes transmitter release that produces subthreshold EPSPs that would not normally yield LTP--are paired with strong depolarization of the postsynaptic CA1 cell, the activated Schaffer collateral synapses undergo LTP.
- This increase in synaptic transmission occurs only if the paired activities of the presynaptic and postsynaptic cells are tightly linked in time, such that the strong postsynaptic depolarization occurs within about 100 ms of transmitter release from the Schaffer collaterals.
- This indicates that the involvement of a **coincidence detector** that allows LTP to occur only when both presynaptic and postsynaptic neurons are active.

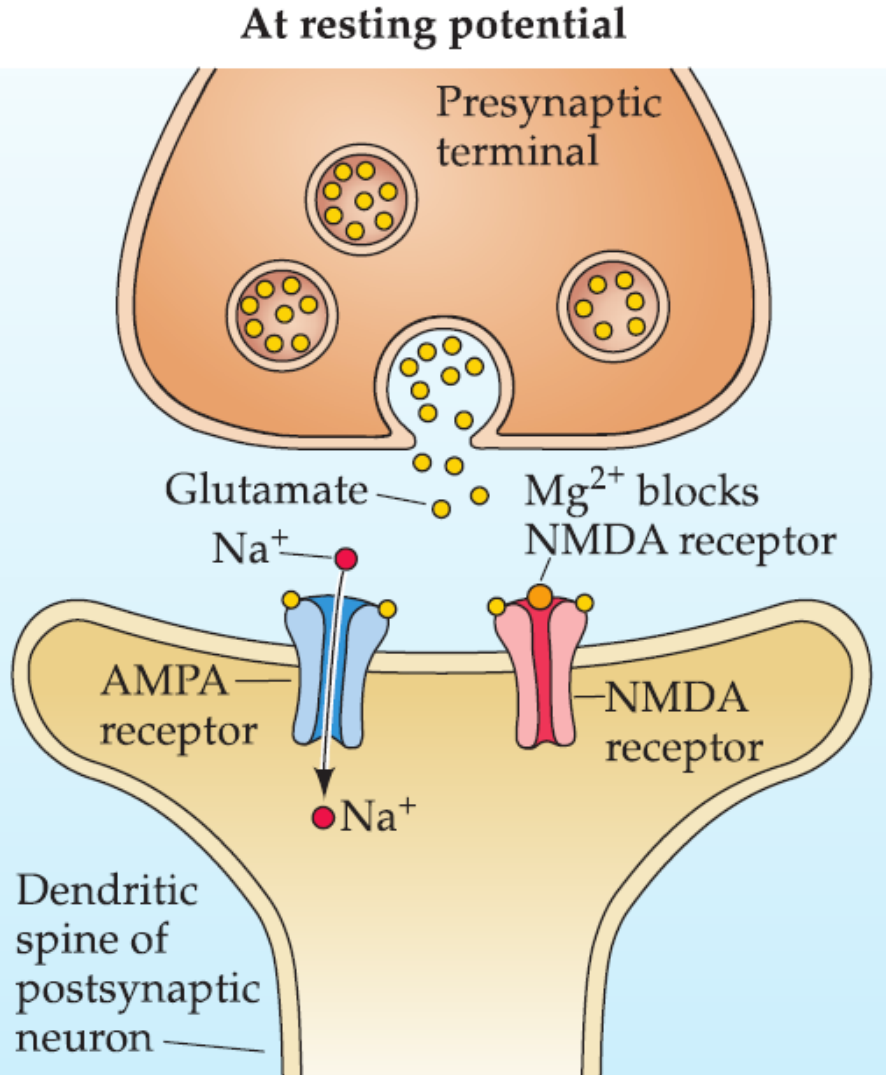
Properties of LTP in Schaffer collateral-CA1 synapses

2. LTP is input specific: When LTP is induced by activation of one synapse, it does not occur in other, inactive synapses that contact the same neuron.
   - LTP is restricted to activated synapses rather than to all of the synapses on a given cell.
3. Associativity.
   - Weak stimulation of a pathway will not by itself trigger LTP.
   - If one pathway is weakly activated at the same time that a neighboring pathway onto the same cell is strongly activated, both synaptic pathways undergo LTP.
   - This selective enhancement of conjointly activated sets of synaptic inputs is often considered a cellular analog of associative learning, where two stimuli are required for learning to take place.



Mechanisms underlying LTP

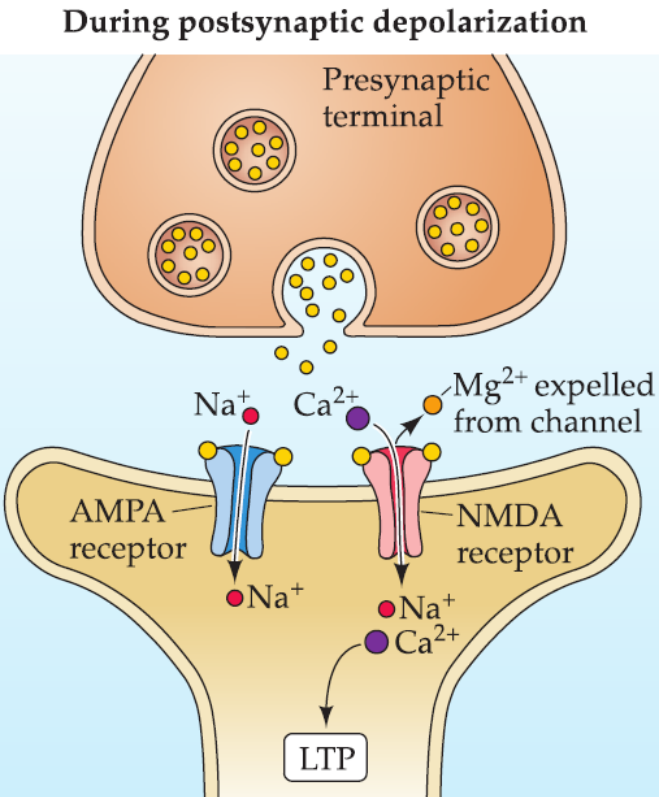
- The NMDA receptor channel is permeable to Ca^{2+}, but is blocked by Mg^{2+}.
- This property provides a critical insight into how LTP is selectively induced by high-frequency activity.



- During low-frequency synaptic transmission, glutamate released by the Schaffer collaterals binds to both NMDA-type and AMPA/kainate-type glutamate receptors.
- While both types of receptors bind glutamate, if the postsynaptic neuron is at its normal resting membrane potential, the pore of the NMDA receptor channel will be blocked by Mg^{2+} ions and no current will flow.
- Under such conditions, the EPSP will be mediated entirely by the AMPA receptors.

Mechanisms underlying LTP

- Because blockade of the NMDA receptor by Mg^{2+} is voltage-dependent, the function of the synapse changes when the postsynaptic cell is depolarized.
- High-frequency stimulation will cause summation of EPSPs, leading to a prolonged depolarization that expels Mg^{2+} from the NMDA channel pore.
- Removal of Mg^{2+} allows Ca^{2+} to enter the postsynaptic neuron, and the resulting increase in Ca^{2+} concentration within the dendritic spines of the postsynaptic cell turns out to be the trigger for LTP.



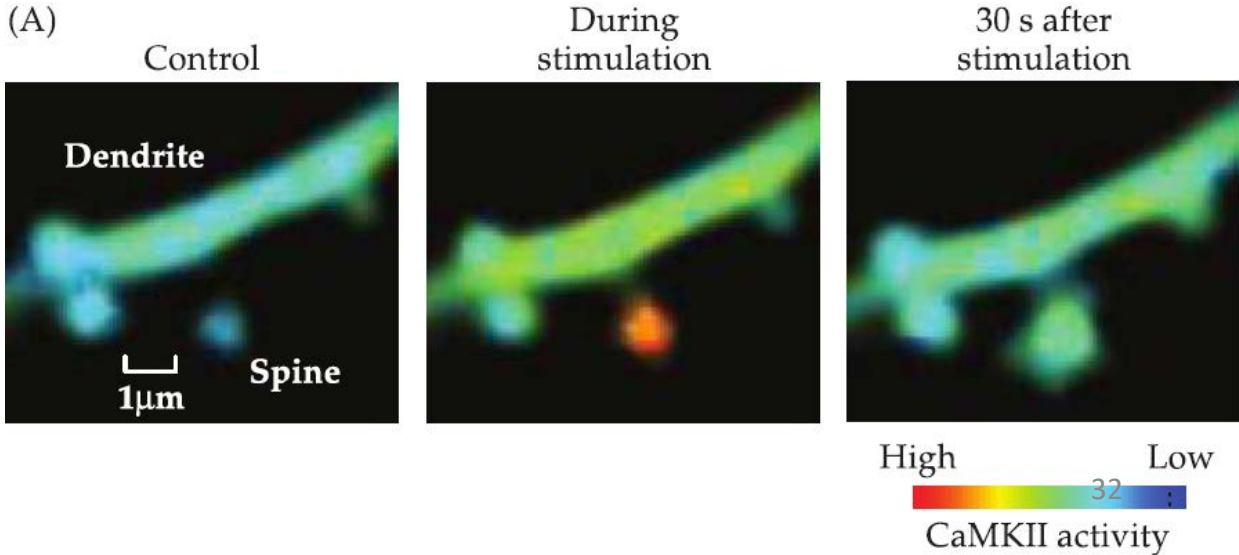
- The NMDA receptor thus behaves like a molecular **coincidence detector**: The channel of this receptor opens (to induce LTP) only when two events occur simultaneously: glutamate is bound to the receptor, and the postsynaptic cell is depolarized to relieve the Mg^{2+} block of the channel pore.

Mechanisms underlying LTP

- These properties of the NMDA receptor can account for many of the characteristics of LTP:
  - The requirement for strong coincident presynaptic and postsynaptic activity to induce LTP arises because presynaptic activity releases glutamate, while the coincident postsynaptic depolarization relieves the Mg^{2+} block of the NMDA receptor.
  - The specificity of LTP can be explained by the fact that NMDA channels will be opened only at synaptic inputs that are active and releasing glutamate, thereby confining LTP to these sites even though EPSPs generated at active synapses depolarize the postsynaptic neuron.
  - With respect to associativity, a weakly stimulated input releases glutamate but cannot sufficiently depolarize the postsynaptic cell to relieve the Mg^{2+} block.
    - If neighboring inputs are strongly stimulated, they provide the "associative" depolarization necessary to relieve the block.

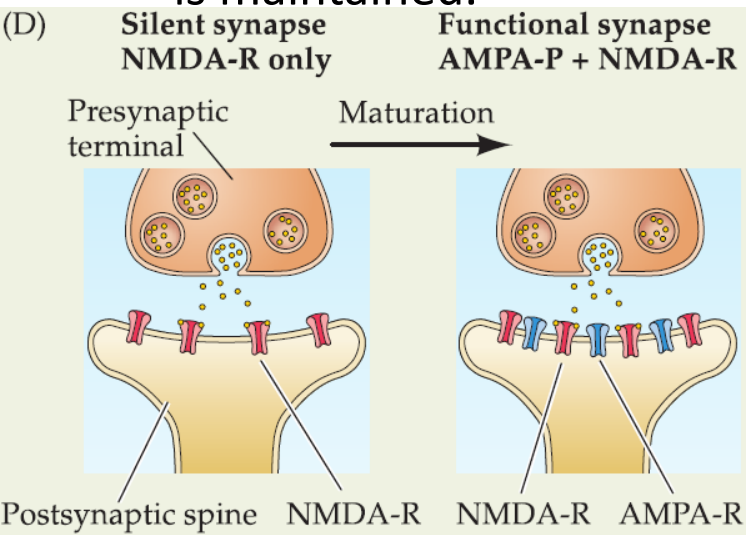
Mechanisms underlying LTP

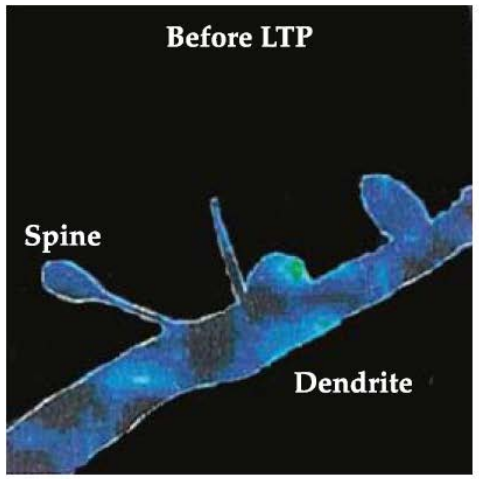
- Several sorts of observations have confirmed that a rise in the concentration of Ca^{2+} in the postsynaptic CA1 neuron--the result of Ca^{2+} entering through NMDA receptors--serves as a second messenger signal that induces LTP.
  - Imaging studies have shown that activation of NMDA receptors causes increases in postsynaptic Ca^{2+} levels.
  - Injection of Ca^{2+} chelators blocks LTP induction, whereas elevation of Ca^{2+} levels in postsynaptic neurons potentiates synaptic transmission.
  - In the postsynaptic neuron, Ca^{2+} induces LTP by activating complicated signal transduction cascades that include at least two Ca^{2+}-activated protein kinases: Ca^{2+}/calmodulin-dependent protein kinase (CaMKII) and protein kinase C (PKC).
    - CaMKII is activated during stimuli that induce LTP, and pharmacological inhibition or genetic deletion of CaMKII prevents LTP.

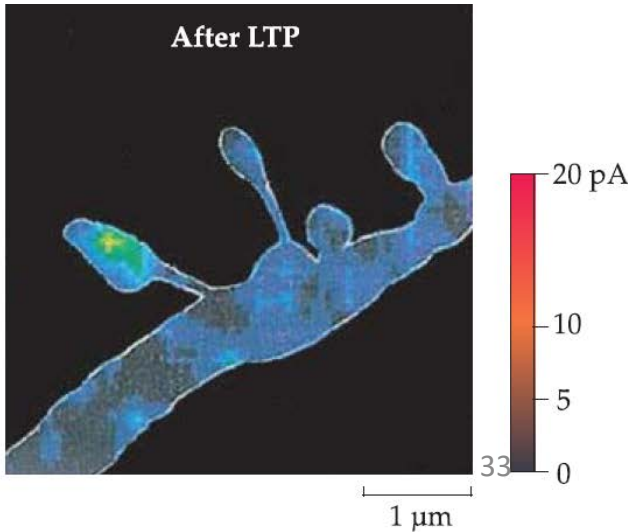


Mechanisms underlying LTP

- The strengthening of synaptic transmission during LTP arises from an increase in the sensitivity of the postsynaptic cell to glutamate.
- Excitatory synapses can dynamically regulate their postsynaptic glutamate receptors and can even add new AMPA receptors to “silent” synapses that did not previously have postsynaptic AMPA receptors.
  - The “expression” or maintenance of LTP apparently is due to such insertion of AMPA receptors into the postsynaptic membrane (as opposed to "induction“ of LTP, which relies on activation of NMDA receptors).
  - The resulting increase in the density of AMPA receptors in the postsynaptic spine increases the response of the postsynaptic cell to released glutamate, yielding a strengthening of synaptic transmission that can last for as long as LTP is maintained.

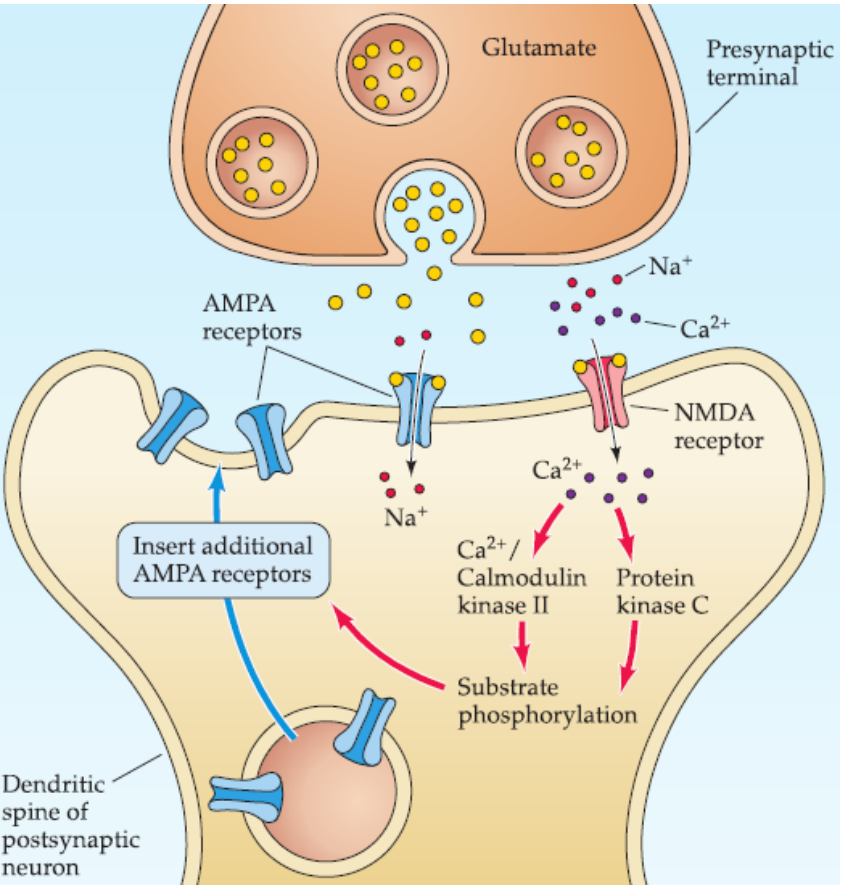






Mechanisms underlying LTP

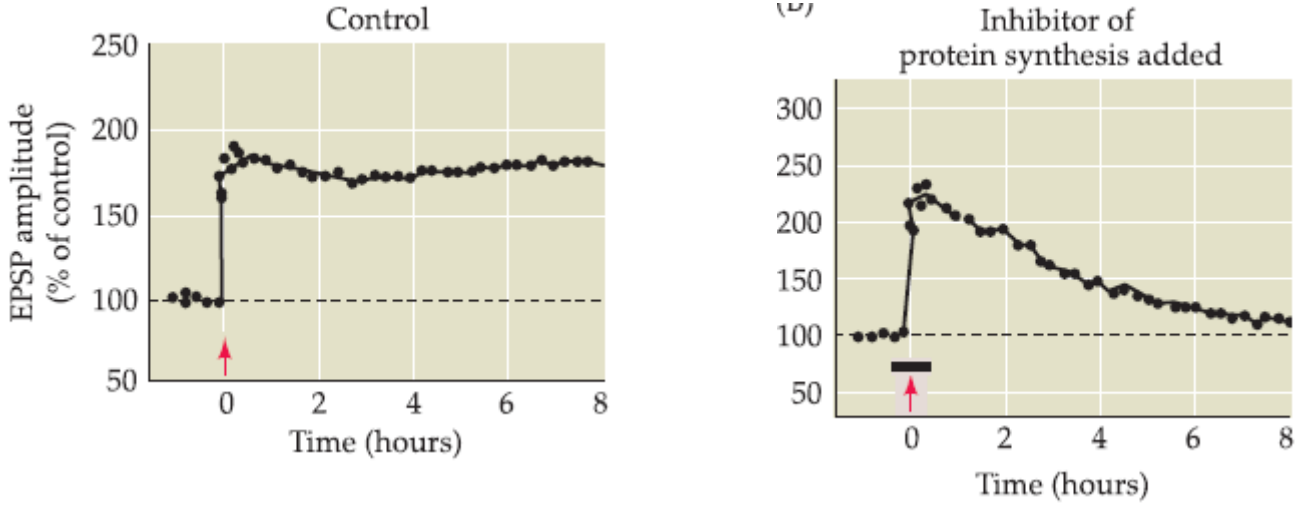
- Summary for the molecular signaling pathways involved in LTP at the Schaffer collateral-CA1 synapse:
  - During glutamate release, the NMDA channel opens only if the postsynaptic cell is sufficiently depolarized.
  - The Ca^{2+} ions that enter the cell through the channel activate postsynaptic protein kinases such as CaMKII and PKC.



- These postsynaptic kinases trigger a series of reactions that lead to insertion of new AMPA receptors into the postsynaptic spine and an increase in the spine's sensitivity to glutamate.
- Under some circumstances, LTP also can increase the ability of presynaptic terminals to release glutamate.
- Because LTP clearly is triggered by the actions of Ca^{2+} within the postsynaptic neuron, this potentiation of presynaptic function requires the spread of a retrograde signal (perhaps NO) from the postsynaptic spine back to the presynaptic terminals.

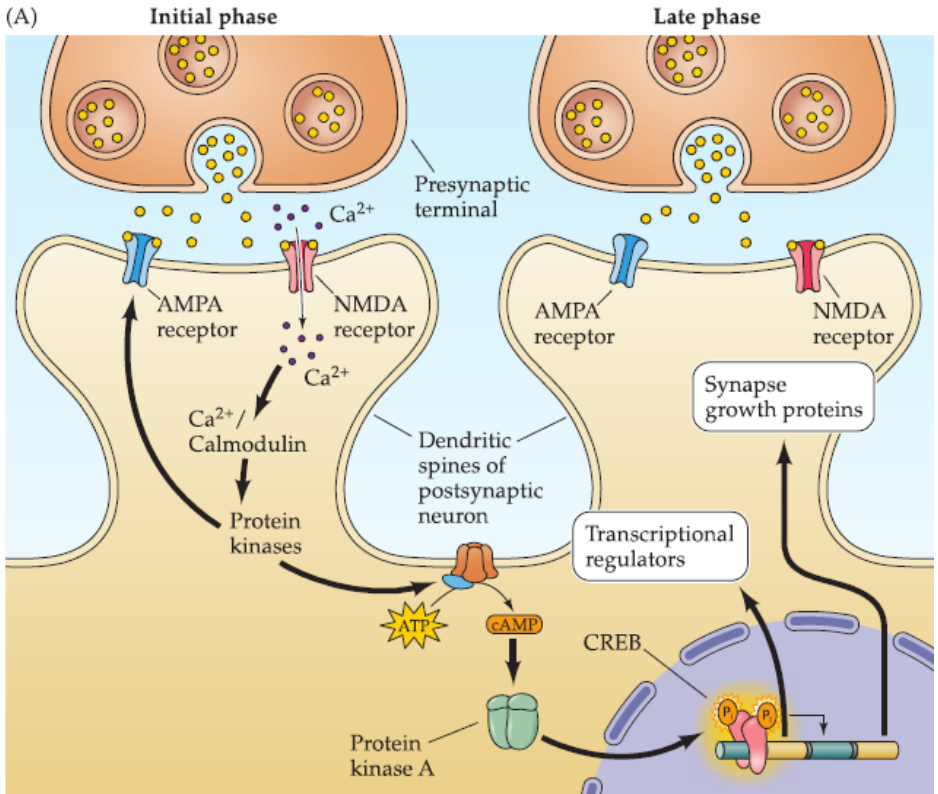
Mechanisms underlying a later phase of LTP

- There is also a later phase of LTP that depends on changes in gene expression and the synthesis of new proteins.
- The contributions of this late phase can be observed by treating synapses with drugs that inhibit protein synthesis:
  - Repetitive high-frequency stimulation induces LTP that persists for many hours.
  - Treatment with anisomycin, an inhibitor of protein synthesis, causes LTP to decay within a few hours after the high-frequency stimulation.



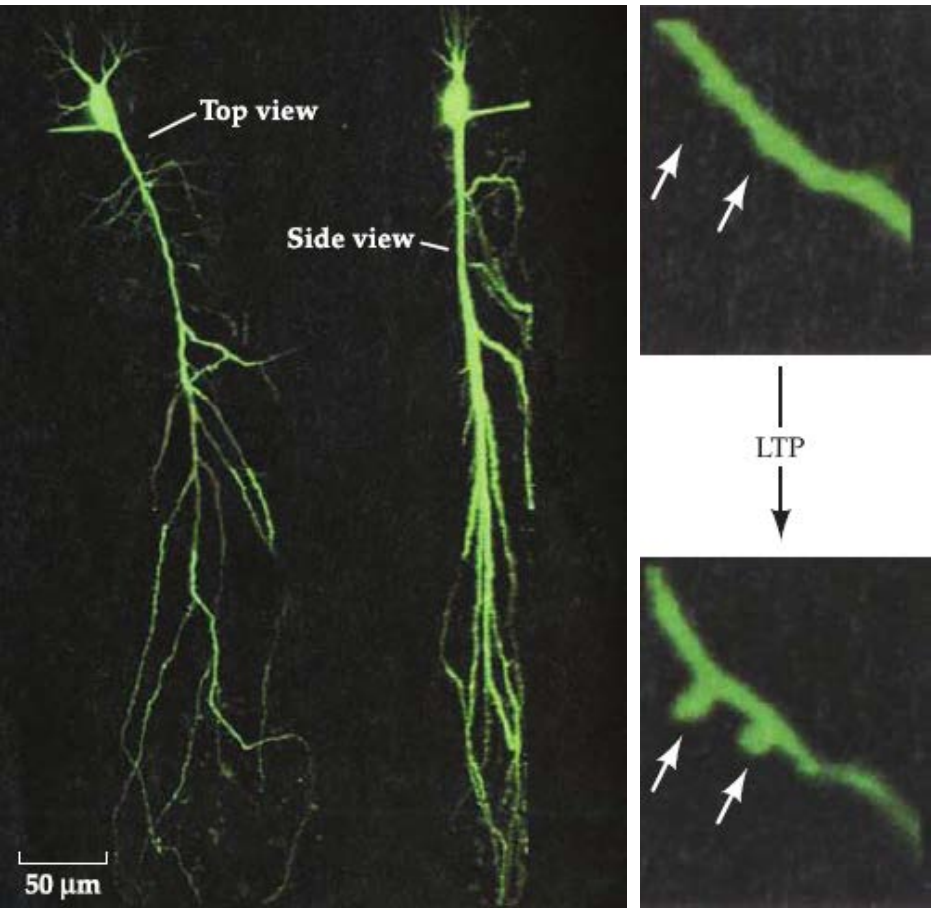
Mechanisms underlying a later phase of LTP

- This late phase of LTP appears to be initiated by protein kinase A, which goes on to activate transcription factors such as CREB, which stimulate the expression of other proteins.
- Although most of these newly synthesized proteins have not yet been identified, they include other transcriptional regulators, protein kinases, and AMPA receptors.



Mechanisms underlying a later phase of LTP

- There is evidence that the number and size of synaptic contacts increases during LTP.
- It is likely that some of the proteins newly synthesized during the late phase of LTP are involved in construction of new synaptic contacts that serve to make LTP essentially permanent.

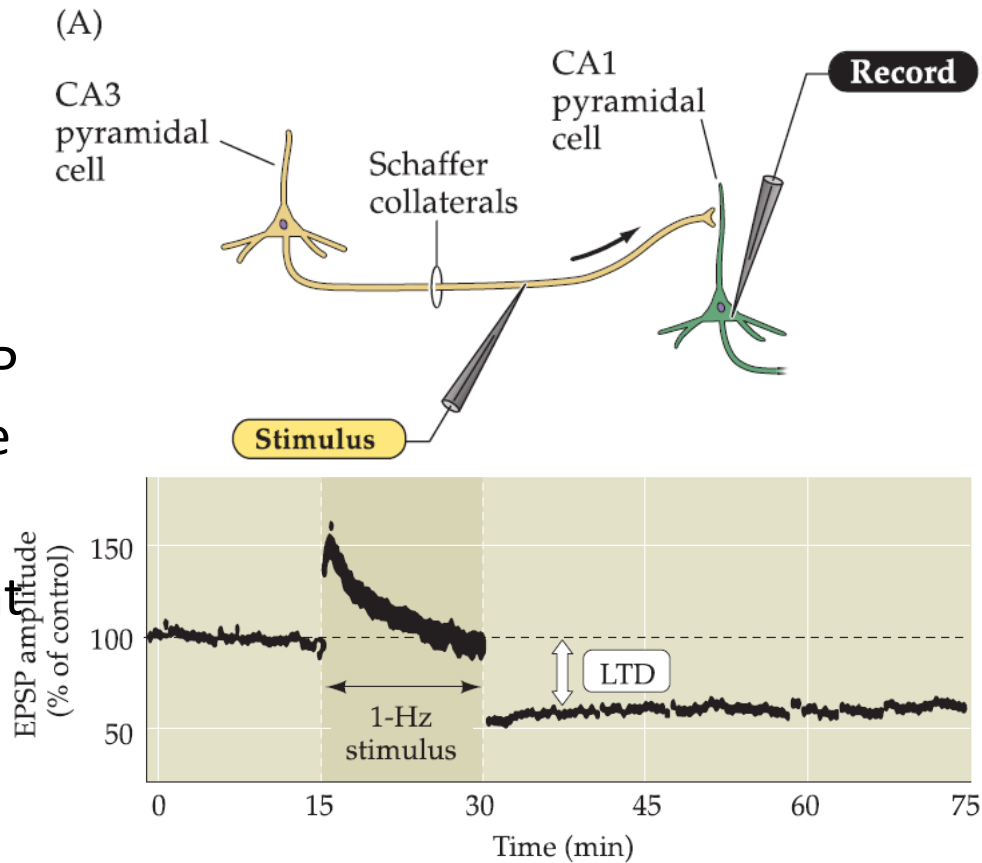


LTP in *Aplysia* and mammalian hippocampus

- Both consist of an early, transient phase that relies on protein kinases to produce posttranslational changes in membrane channels.
- Both have later, long-lasting phases that require changes in gene expression mediated by CREB.
- Both forms of long-term synaptic plasticity are likely to be involved in long-term storage of information, although the role of LTP in memory storage in the hippocampus is not firmly established.

Mechanisms underlying LTD

- LTD was found to occur at the synapses between the Schaffer collaterals and the CA1 pyramidal cells in the hippocampus in the late 1970s.
- LTP at these synapses requires brief, high-frequency stimulation.
- LTD occurs when the Schaffer collaterals are stimulated at a low rate--about 1 Hz--for long periods (10-15 minutes).
- This pattern of activity depresses the EPSP for several hours and, like LTP, is specific to the activated synapses.
- LTD can erase the increase in EPSP size due to LTP, and, conversely, LTP can erase the decrease in EPSP size due to LTD.
- This complementarity suggests that LTD and LTP reversibly affect synaptic efficiency by acting at a common site.

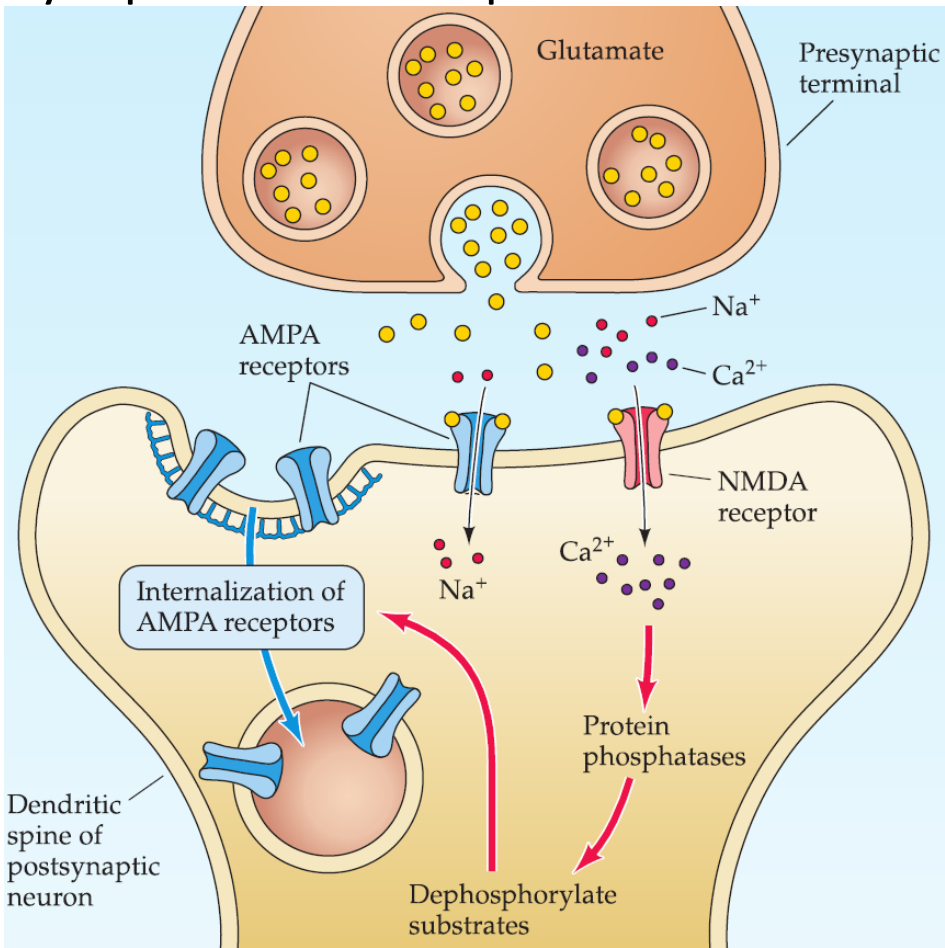


Key elements shared by LTP and LTD

- Both require activation of NMDA-type glutamate receptors and the resulting entry of Ca^{2+} into the postsynaptic cell.
- The major determinant of whether LTP or LTD arises appears to be the nature of the Ca^{2+} signal in the postsynaptic cell:
  - Small and slow rises in Ca^{2+} lead to depression.
  - Large and fast increases in Ca^{2+} trigger potentiation.
- Modification of target proteins in LTP and LTD:
  - LTP is at least partially due to activation of protein kinases, which phosphorylate their target proteins.
  - LTD, on the other hand, appears to result from activation of Ca^{2+}-dependent phosphatases that cleave phosphate groups from these target molecules.
    - Evidence in support of this idea is that phosphatase inhibitors prevent LTD, but do not block LTP.
- The different effects of Ca^{2+} during LTD and LTP may arise from the selective activation of protein phosphatases and kinases by the different types of Ca^{2+} signals.

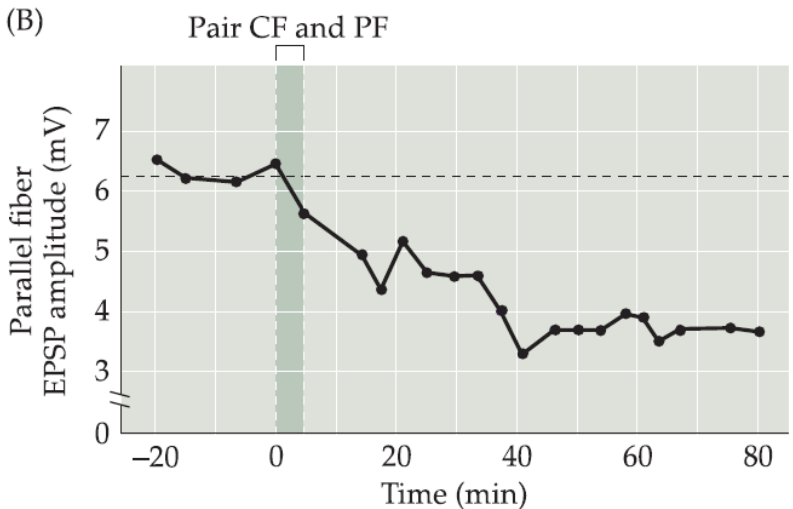
Mechanisms underlying LTD

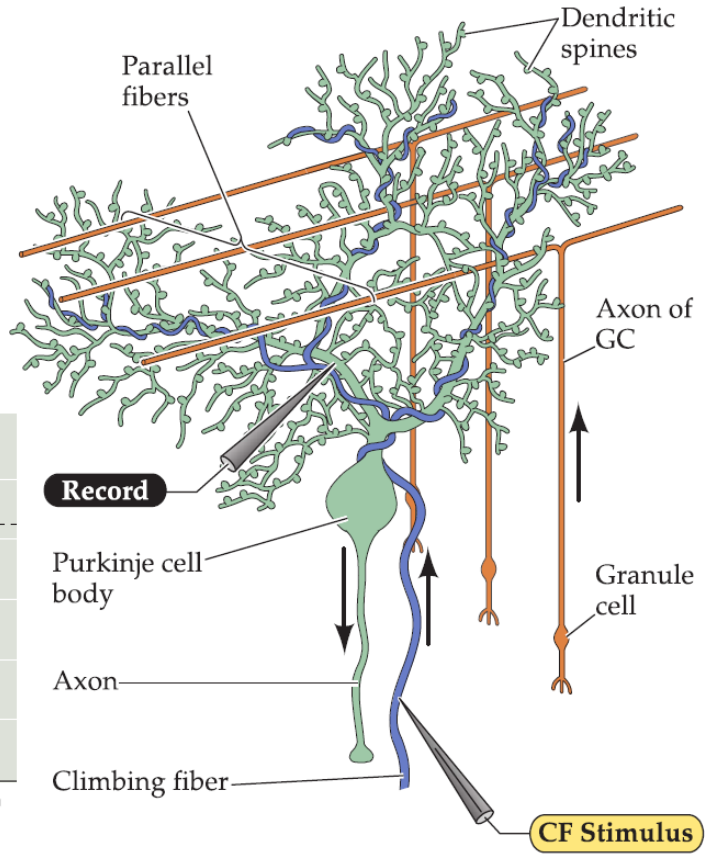
- It is possible that LTP and LTD phosphorylate and dephosphorylate the same set of regulatory proteins to control the efficacy of transmission at the Schaeffer collateral-CA1 synapse.
- Just as LTP at this synapse is associated with insertion of AMPA receptors, LTD is often associated with a loss of synaptic AMPA receptors.
- This loss probably arises from internalization of AMPA receptors into the postsynaptic cell, due to the same sort of clathrin-dependent endocytosis mechanisms important for synaptic vesicle recycling in the presynaptic terminal.



LTD in the cerebellum

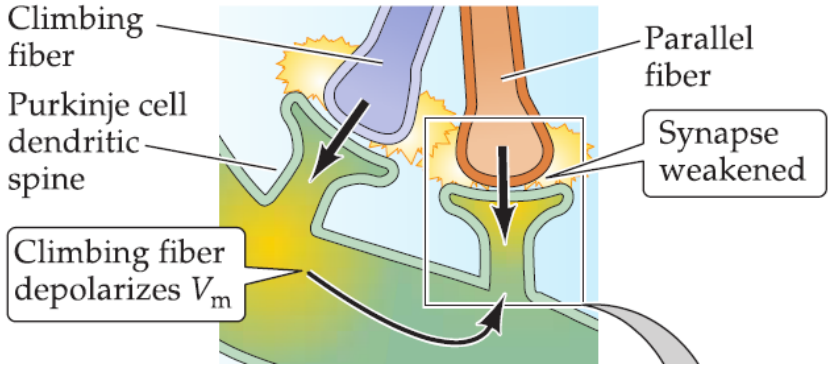
- LTD of synaptic inputs onto cerebellar Purkinje cells was first described by Masao Ito and his colleagues in Japan in the early 1980s.
- Purkinje neurons in the cerebellum receive two distinct types of excitatory input: climbing fibers and parallel fibers.
- LTD reduces the strength of transmission at the parallel fiber synapse and has recently been found to depress transmission at the climbing fiber synapse as well.
- This form of LTD has been implicated in the motor learning that mediates the coordination, acquisition, and storage of complex movements within the cerebellum.

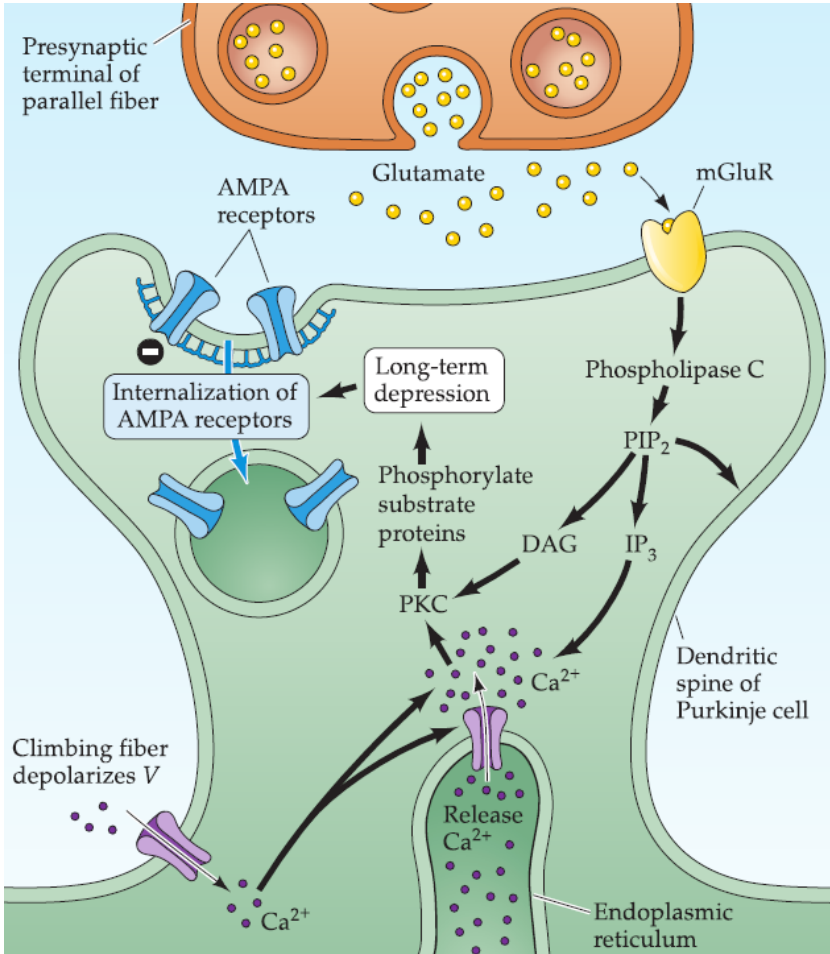




LTD in the cerebellum

- Cerebellar LTD is <u>associative</u> because it occurs only when climbing fibers and parallel fibers are activated at the same time.
- Associativity arises from the combined actions of two distinct intracellular signal transduction pathways that are activated in the postsynaptic Purkinje cell due to the activity of climbing fiber and parallel fiber synapses.
  1. Glutamate released from the parallel fiber terminals activates at two types of receptors, the AMPA-type and metabotropic glutamate receptors.
     - Glutamate binding to the AMPA receptor results in membrane depolarization, whereas binding to the metabotropic receptor produces the second messengers inositol trisphosphate (IP_3) and diacylglycerol (DAG).

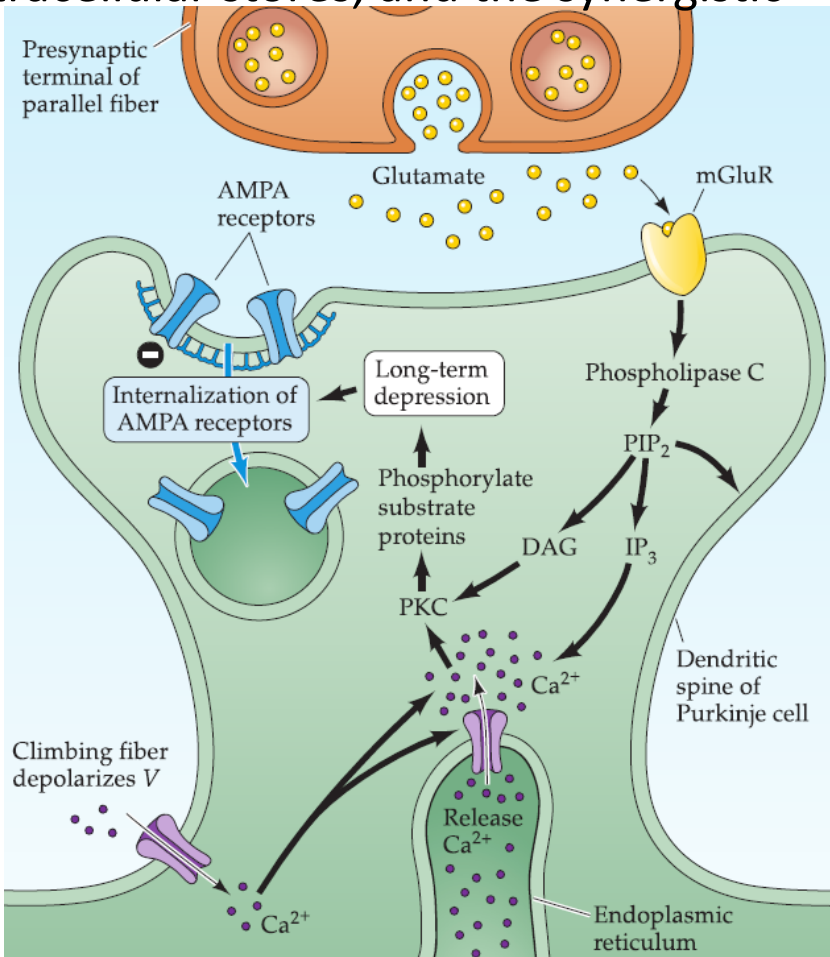




LTD in the cerebellum

2. The second signal transduction pathway, initiated by climbing fiber activation, causes an influx of Ca^{2+} through voltage-gated channels and a subsequent increase in intracellular Ca^{2+} concentration.

- These second messengers work together to cause an amplified rise in intracellular Ca^{2+} concentration, due to IP3 and Ca^{2+} acting together on IP3 receptors, triggering release of Ca^{2+} from intracellular stores, and the synergistic activation of PKC by Ca^{2+} and DAG.
- The associative property of cerebellar LTD appears to arise from both IP3 receptors and PKC serving as coincidence detectors.
- AMPA receptors are one of the proteins phosphorylated by PKC.
- The consequence of PKC activation is to cause an internalization of AMPA receptors via clathrin-dependent endocytosis.
- This loss of AMPA receptors decreases the response of the post synaptic Purkinje cell to glutamate released from the presynaptic terminals of the parallel fibers.



LTD in the cerebellum and hippocampus

- In contrast to LTD in the hippocampus, cerebellar LTD requires the activity of a protein kinase, rather than a phosphatase, and does not involve Ca^{2+} entry through the NMDA type of glutamate receptor (which is not present in mature Purkinje cells).

- However, the net effect is the same in both cases: internalization of AMPA receptors is a common mechanism for decreased efficacy of both hippocampal and cerebellar synapses during LTD.

Summary for synaptic plasticity

- Synapses exhibit many forms of plasticity that occur over a broad temporal range.
- At the shortest times (seconds to minutes), facilitation, augmentation, potentiation, and depression provide rapid but transient modifications in synaptic transmission.
  - These forms of plasticity change the amount of neurotransmitter released from presynaptic terminals and are based on alterations in Ca^{2+} signaling and synaptic vesicle pools at recently active terminals.
- Longer-lasting forms of synaptic plasticity such as LTP and LTD are also based on Ca^{2+} and other intracellular second messengers.
  - At least some of the synaptic changes produced by these long-lasting forms of plasticity are postsynaptic, caused by changes in neurotransmitter receptor trafficking, although alterations in neurotransmitter release from the presynaptic terminal can also occur.
  - In these more enduring forms of plasticity, protein phosphorylation and changes in gene expression greatly outlast the period of synaptic activity and can yield changes in synaptic strength that persist for hours, days, or even longer.