Learning & Memory

Learning is the process by which new information is acquired; memory is the process by which that knowledge is retained.
http://www.unmc.edu/physiology/Mann/mann19.html

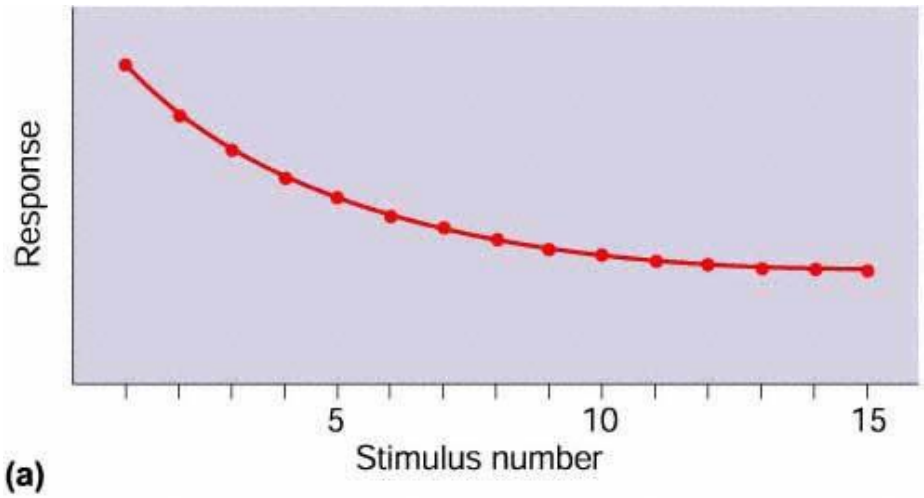
학습

Procedural (절차학습) (cf. 서술기억): 자극에 의한 행동의 변화
감각과 운동을 연결하는 기억형성

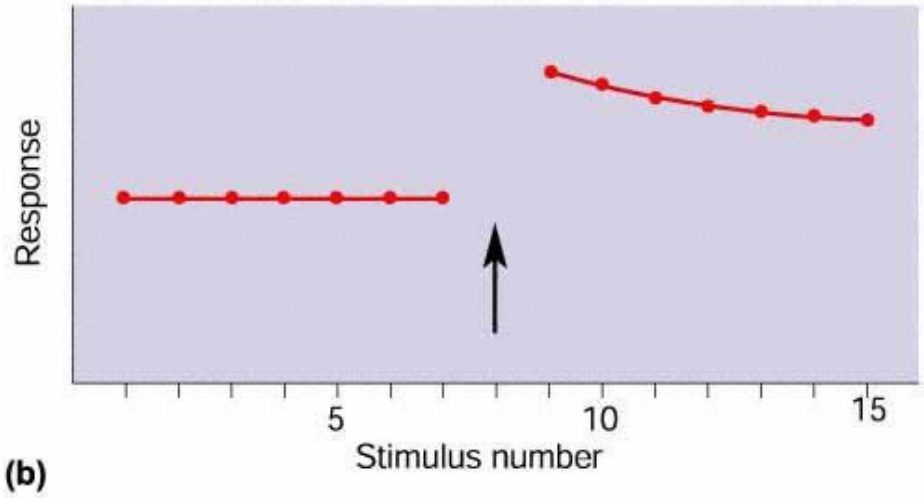
Non-associative (비연합학습): habituation (습관화)
sensitization (민감화)

Associative (연합학습): classical conditioning (고전적 조건화)
instrumental conditioning (도구적 조건화)

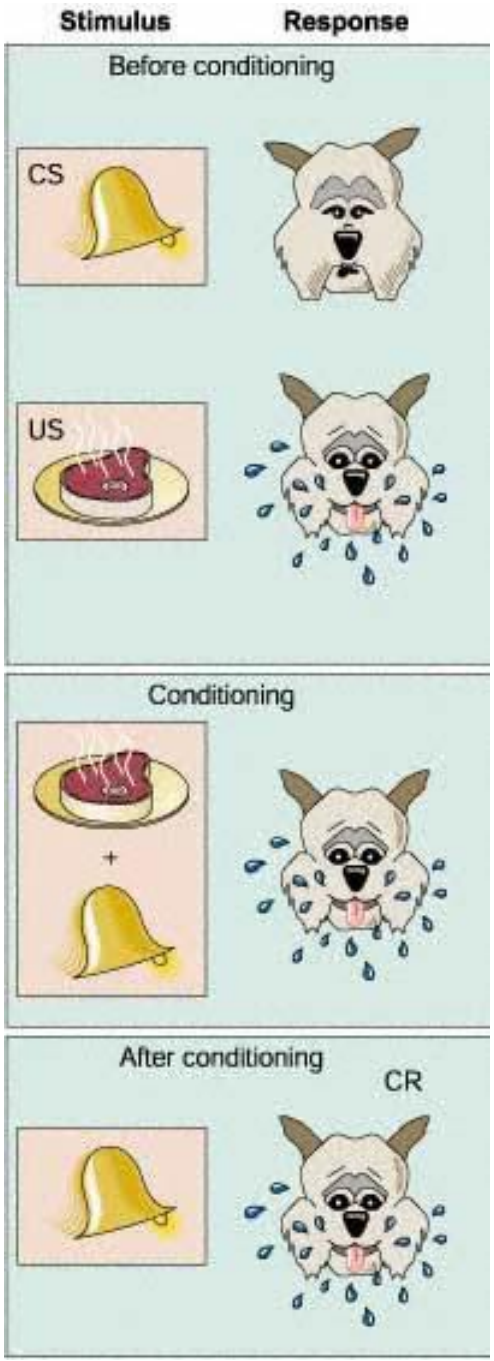
Non-associative



habituation

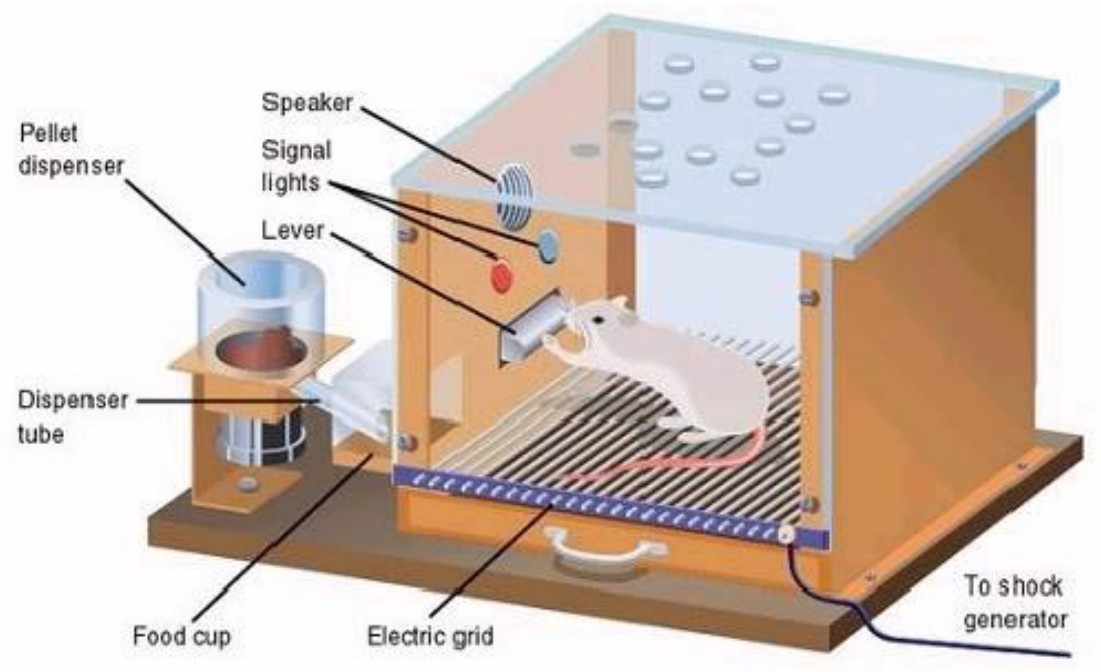


sensitization



Associative

Instrumental (operant) conditioning

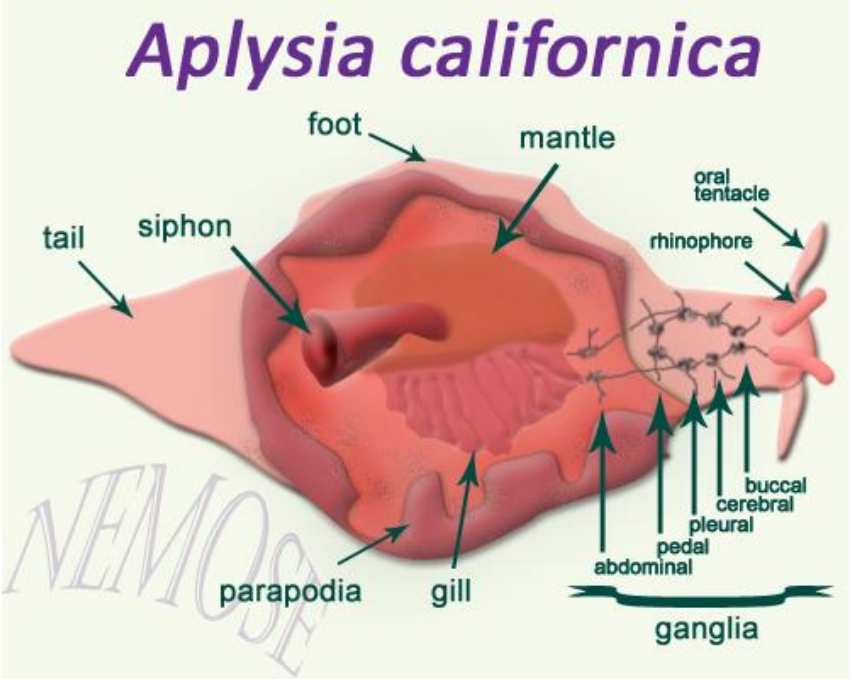


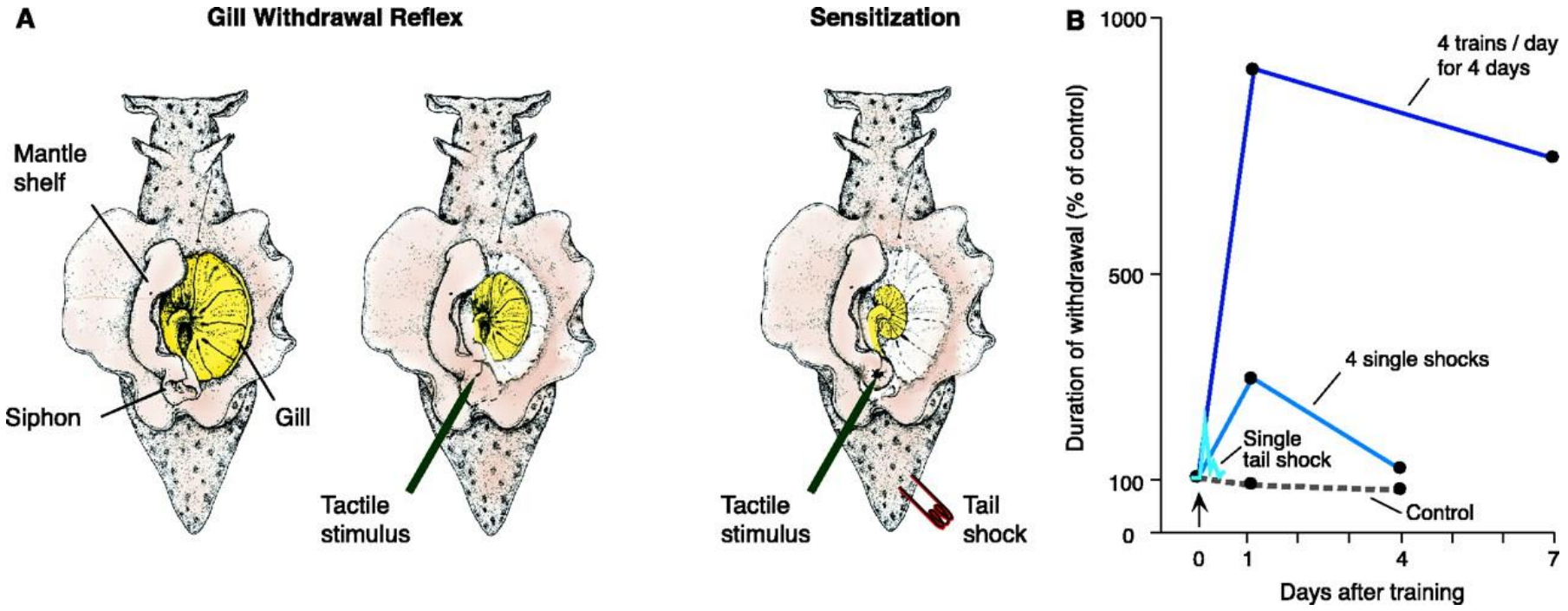
Operant conditioning is distinguished from classical conditioning in that operant conditioning deals with the modification of "voluntary behavior" or operant behavior.

Operant behavior "operates" on the environment and is maintained by its consequences, while classical conditioning deals with the conditioning of reflexive (reflex) behaviors which are elicited by antecedent conditions.

Since motivation plays a key role in operant conditioning, the underlying neural circuit is more complex in operant conditioning.

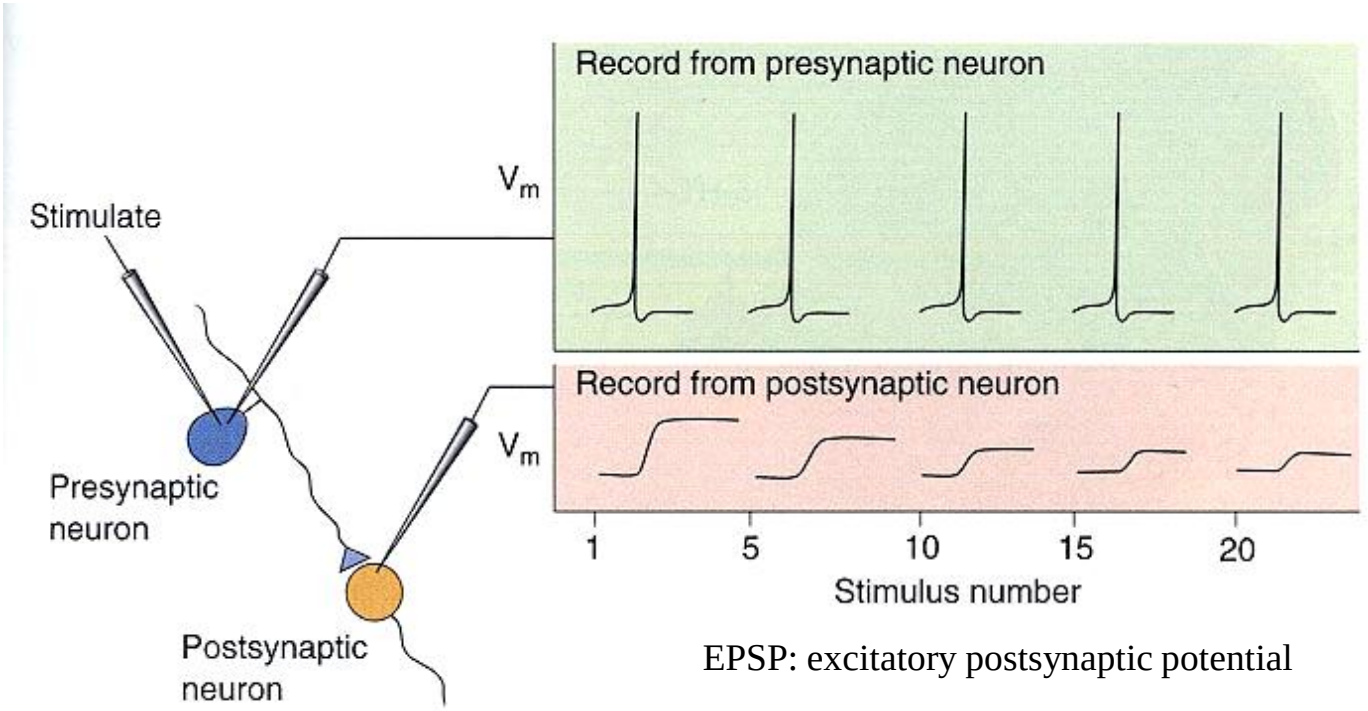
Aplysia study by Dr. Eric Kandel





A simple learned behavior. (A) A dorsal view of Aplysia showing the gill, the animal's respiratory organ. A light touch to the siphon with a fine probe causes the siphon to contract and the gill to withdraw. Here, the mantle shelf is retracted for a better view of the gill. Sensitization of the gill-withdrawal reflex, by applying a noxious stimulus to another part of the body, such as the tail, enhances the withdrawal reflex of both the siphon and the gill. (B) Spaced repeti- tion converts short-term memory into long-term memory in Aplysia. Before sensitization training, a weak touch to the siphon causes only a weak, brief siphon and gill withdrawal reflex. Following a single noxious, sensitizing, shock to the tail, that same weak touch produces a much larger siphon and gill reflex withdrawal response, an enhancement that lasts about 1 hour. More tail shocks increase the size and duration of the response. [Modified from (79)]

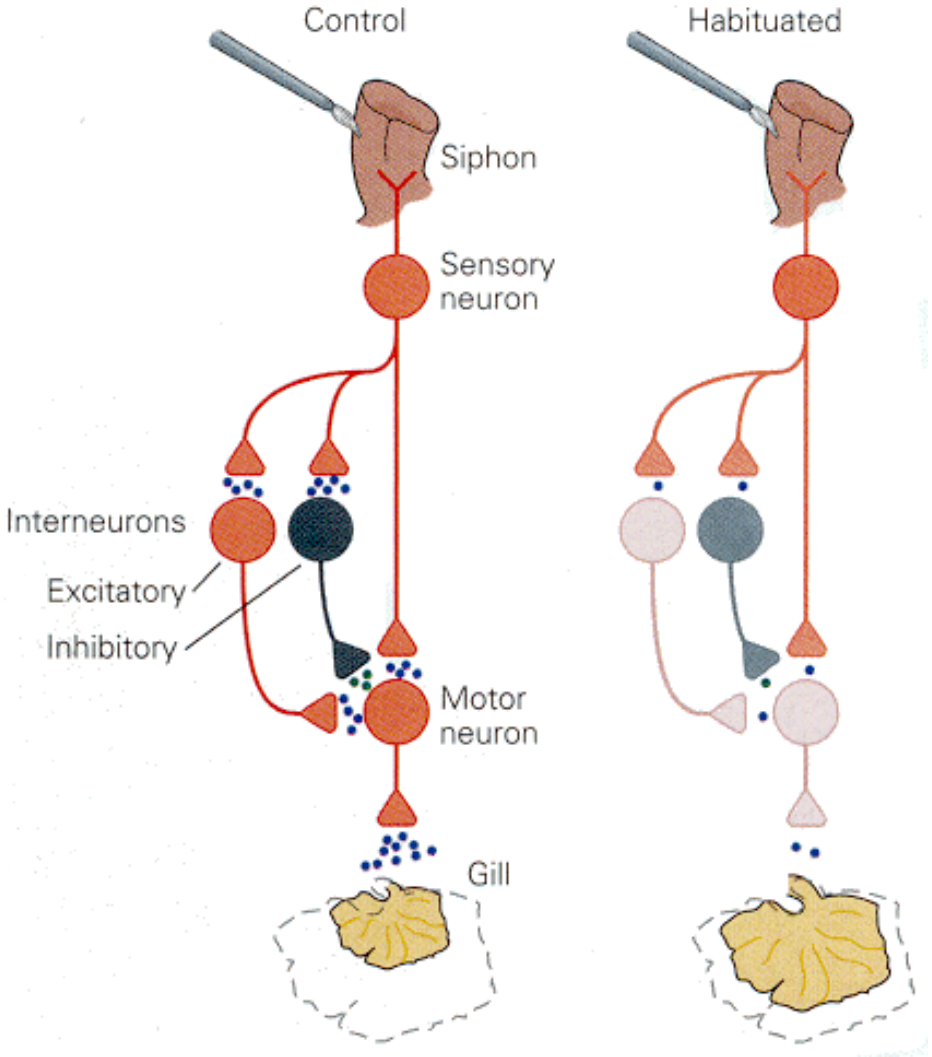
Habituation at the cellular level



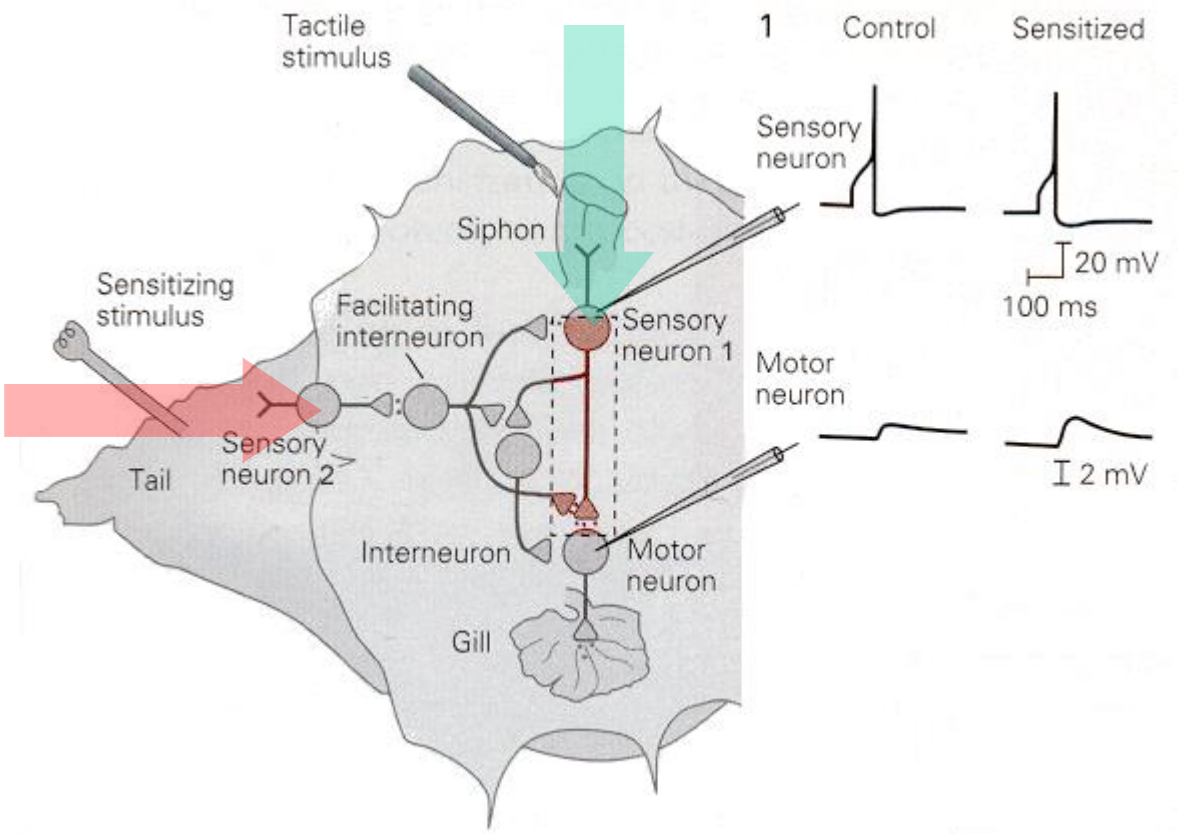
EPSP: excitatory postsynaptic potential

After habituation, fewer quanta per action potential were released. The sensitivity of the postsynaptic cell to NT did not change.

Habituation. Simplified neural circuits involved in the habituation process in *Aplysia*. There are about 24 sensory neurons in the siphon; these are glutaminergic. They synapse on 6 motor neurons that innervate the gill and various interneurons as shown. The control condition is shown on the left, the habituated condition on the right. (Kandel, ER, JH Schwartz and TM Jessell (2000) *Principles of Neural Science*. New York: McGraw-Hill.)



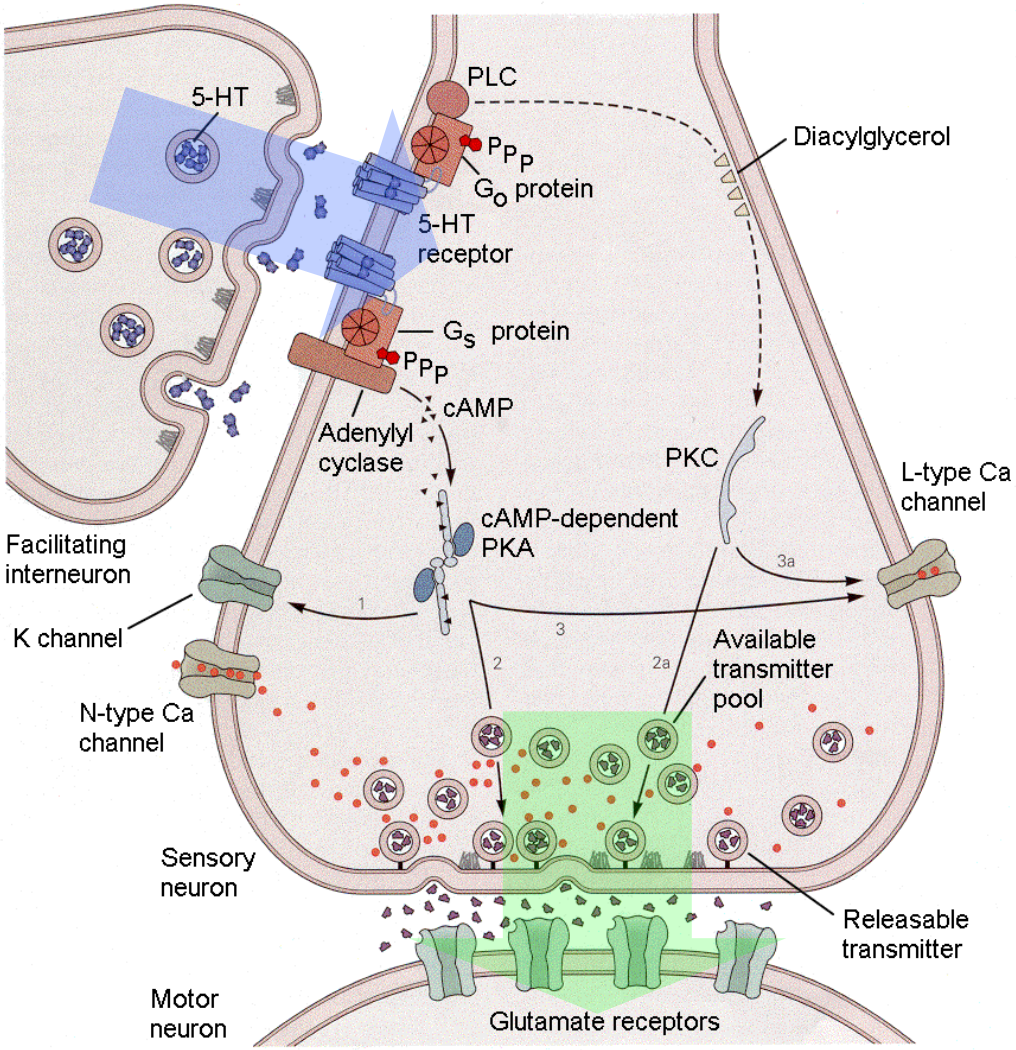
Sensitization. It is produced by applying a noxious stimulus to the tail of the Aplysia's tail, activated sensory neuron 2. This, in turn activates a facilitating interneuron that enhances transmission in the pathway from the siphon to the motor neuron. (Kandel, ER, JH Schwartz and TM Jessell (2000) *Principles of Neural Science*. New York: McGraw-Hill.)



http://www.unmc.edu/Physiology/Mann/mann19.html

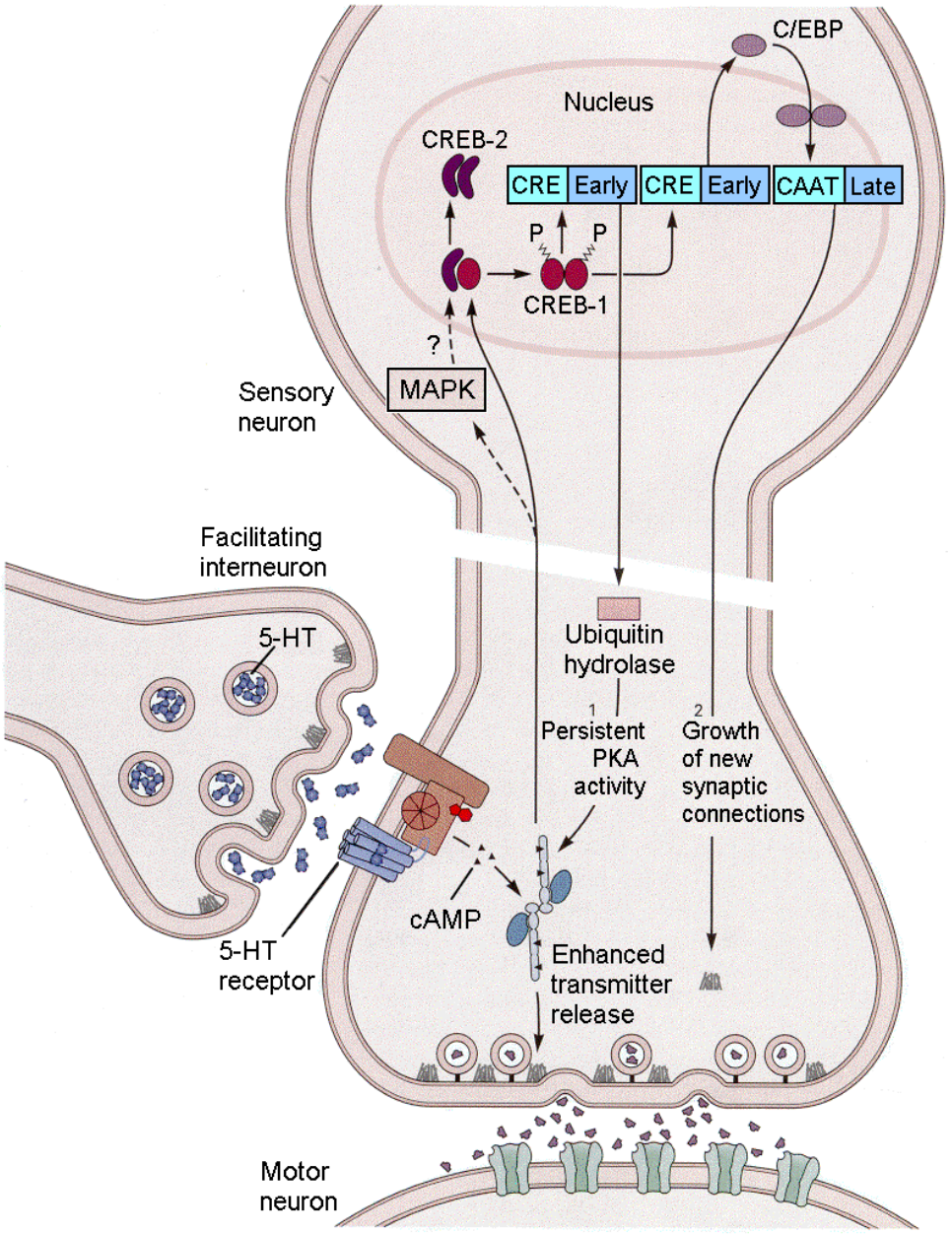
The molecular mechanism of sensitization. The synaptic and chemical events underlying presynaptic facilitation involved in producing sensitization. See text for details. (Kandel, ER, JH Schwartz and TM Jessell (2000) *Principles of Neural Science*. New York: McGraw-Hill.)

5-HT
cAMP
PKA activation
Phosphorylation of K channel
Closing K channel
Increased Ca transport
Increased neurotransmitter release



With only short-term tail stimulation, the sensitization will fairly quickly disappear when tail stimulation ceases. However, the sensitization can be made relatively permanent by repeated tail stimulation. This long-term sensitization (and also long-term habituation) occurs because there are structural changes that occur in the presynaptic terminals (sensory neuron 1, for example). With sensitization, there is an up to 2-fold increase in the number of synaptic terminals in both sensory and motorneurons. Alternatively, with habituation, there is a one-third reduction in the number of synaptic terminals. Both of these changes require altered protein synthesis by mechanisms shown in Fig. 19-7.

Fig. 19-7 - Long-term storage of implicit memory for sensitization involves changes shown in Fig. 19-6 plus changes in protein synthesis that result in formation of new synaptic connections. (Kandel, ER, JH Schwartz and TM Jessell (2000) *Principles of Neural Science*. New York: McGraw-Hill.)



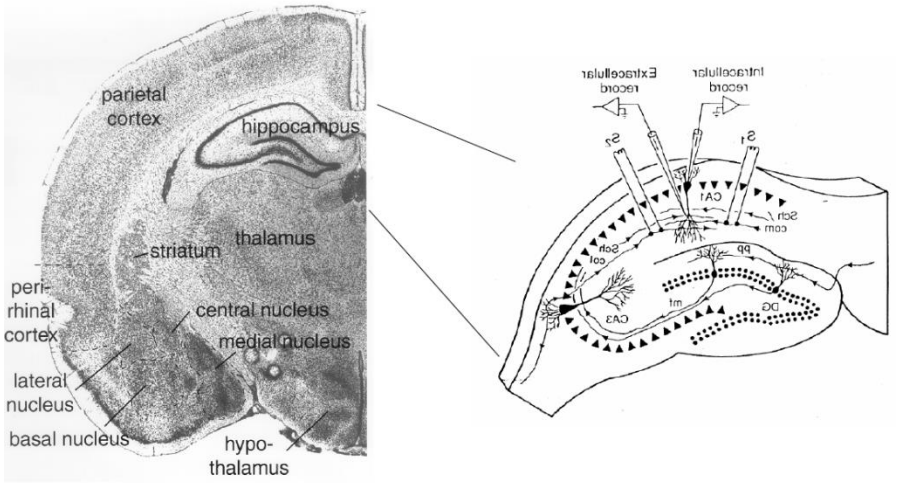
Learning

Long-term potentiation: http://en.wikipedia.org/wiki/Long-term_potentiation

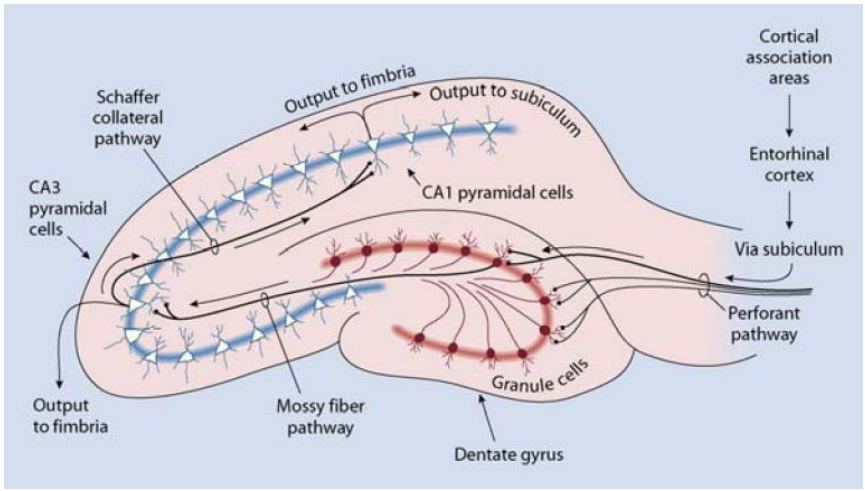
Discovered by Lomo (1966)
A long-term increase in the excitability of a neuron to a particular synaptic input caused by repeated high-frequency activity of that input.

Mechanisms of Synaptic Plasticity
Induction of Long-Term Potentiation: For Associative Conditioning

Learning in a Dish: Hippocampal Slice



Bliss and Lomo (1973)



<u>Some conclusions from LTP experiments</u>

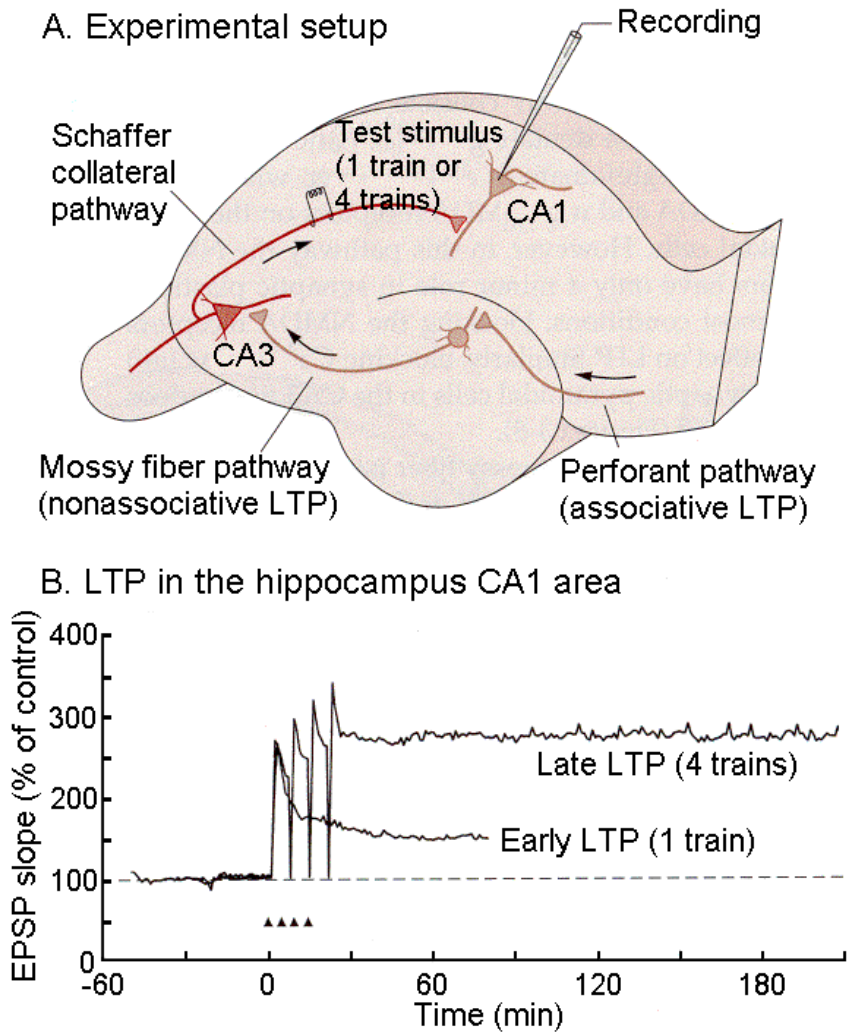
LTP is a synapse specific

LTP requires activation of post-synaptic cell: only if both pre- and post-synaptic neurons are active at the same time **(Hebbian LTP)**

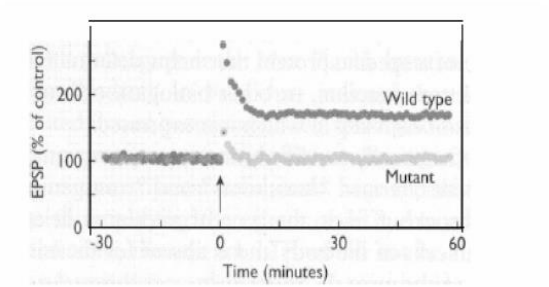
NMDA channel is crucial for induction of LTP but not for maintenance of LTP

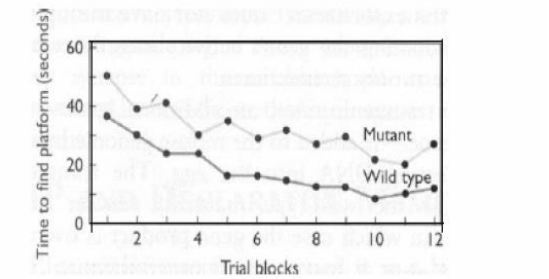
NMDA channel cannot be bypassed by polarizing the cell. Ca influx through NMDA channel is required **(NMDA receptor dependent LTP)**

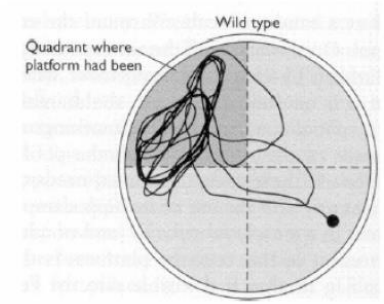
Fig. 19-8 - A. Experimental setup for demonstrating LTP in the hippocampus. The Schaffer collateral pathway is stimulated to cause a response in pyramidal cells of CA1. B. Comparison of EPSP (excitatory postsynaptic potential) size in early and late LTP with the early phase evoked by a single train and the late phase by 4 trains of pulses. (Kandel, ER, JH Schwartz and TM Jessell (2000) *Principles of Neural Science*. New York: McGraw-Hill.)

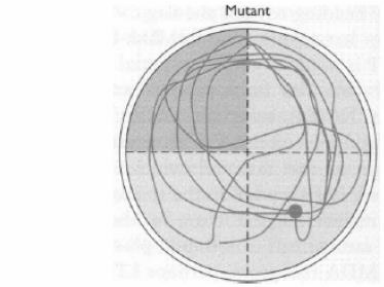


NMDAR-KO Mouse







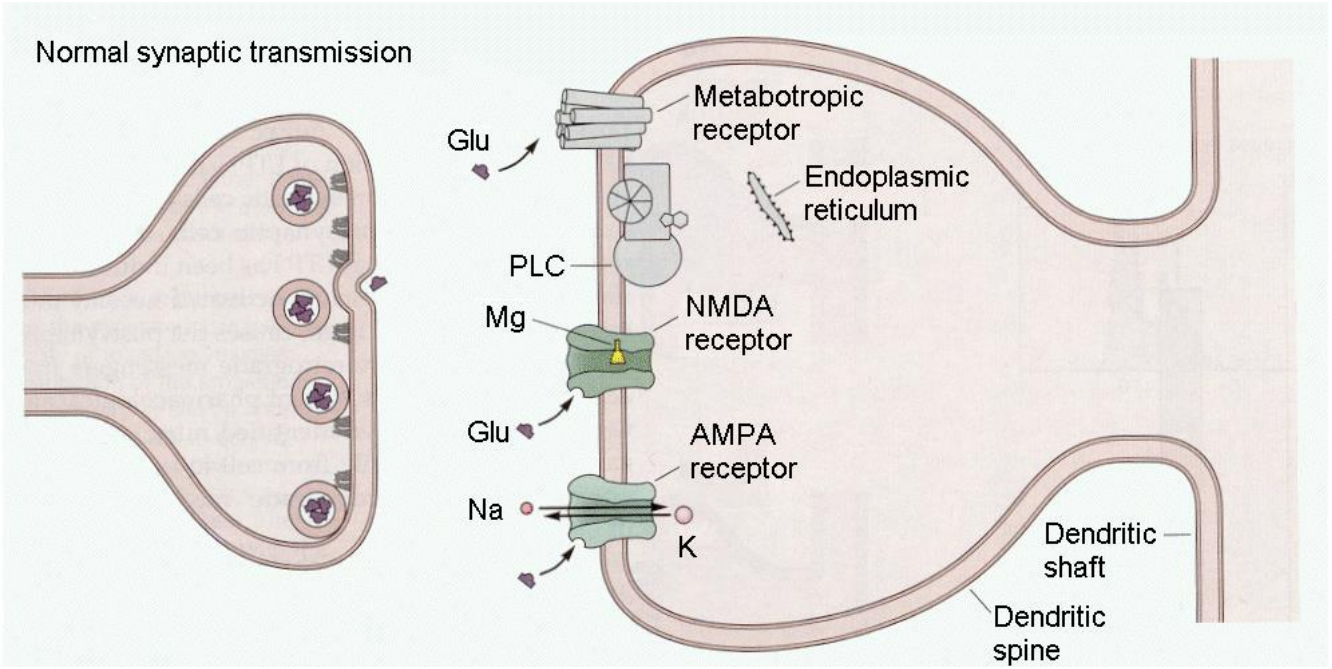


Morris water maze test

No NMDAR → No LTP in Hippocampus → No Spatial Learning

NMDA Receptors
Found in hippocampus CA 1 field
Normally, Mg2+ blocks Ca2+ channel so when glutamate binds to receptor, Ca2+ cannot enter to depolarize cell.
After LTP, Mg2+ ions are displaced so when glutamate binds to receptor, Ca2+ enters cell to depolarize.

Fig. 19-9 - During normal low-frequency trans-mission, glutamate interacts with NMDA and non-NMDA (AMPA) and metabotropic receptors.

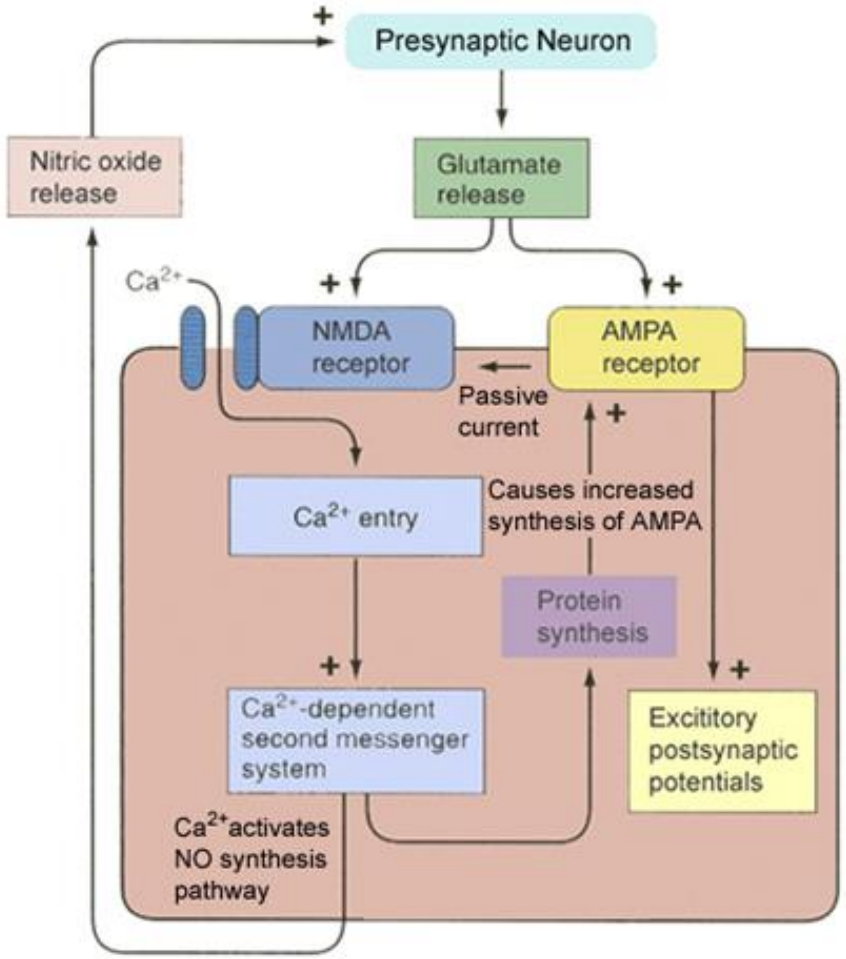


Hebb rule:

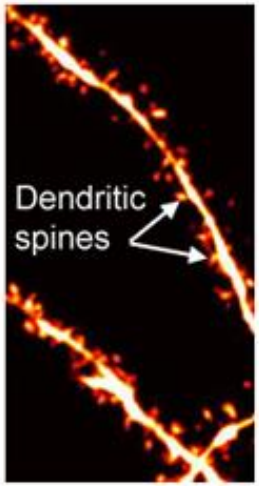
The hypothesis proposed by Donald Hebb that the cellular basis of learning involves strengthening of a synapse that is repeatedly active when the postsynaptic neuron fires.

"Neurons that fire together get wired together."

Long Term Potentiation at the Dendritic Spine

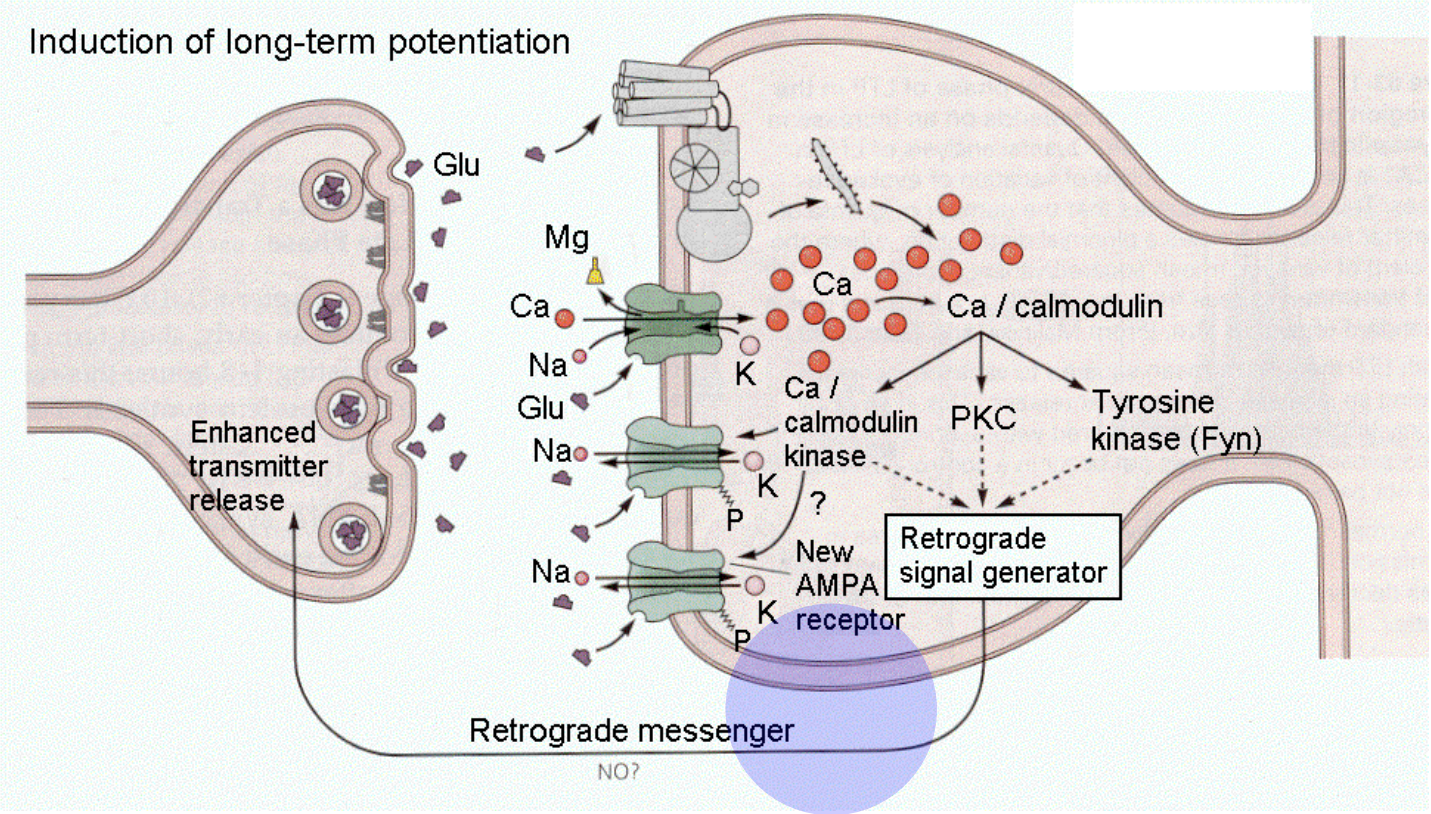


Spine of Postsynaptic Neuron



See also: Fig. 8-30 Silverthorn

Fig. 19-10 - With high-frequency stimulation other events occur as described in the text. (Kandel, ER, JH Schwartz and TM Jessell (2000) *Principles of Neural Science*. New York: McGraw-Hill.)

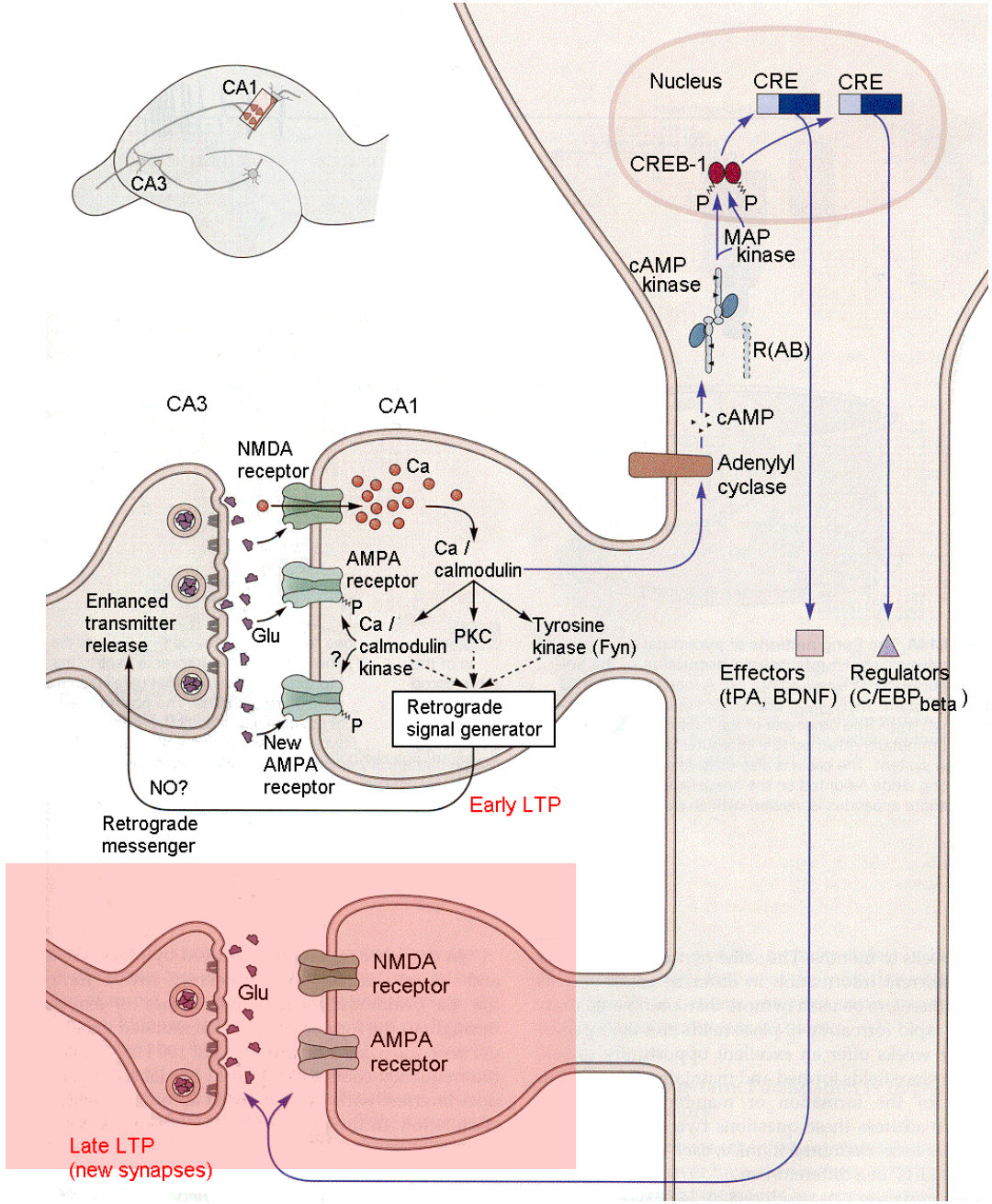


LTP results in the insertion of new AMPA (non NMDA) receptors into the dendrite.

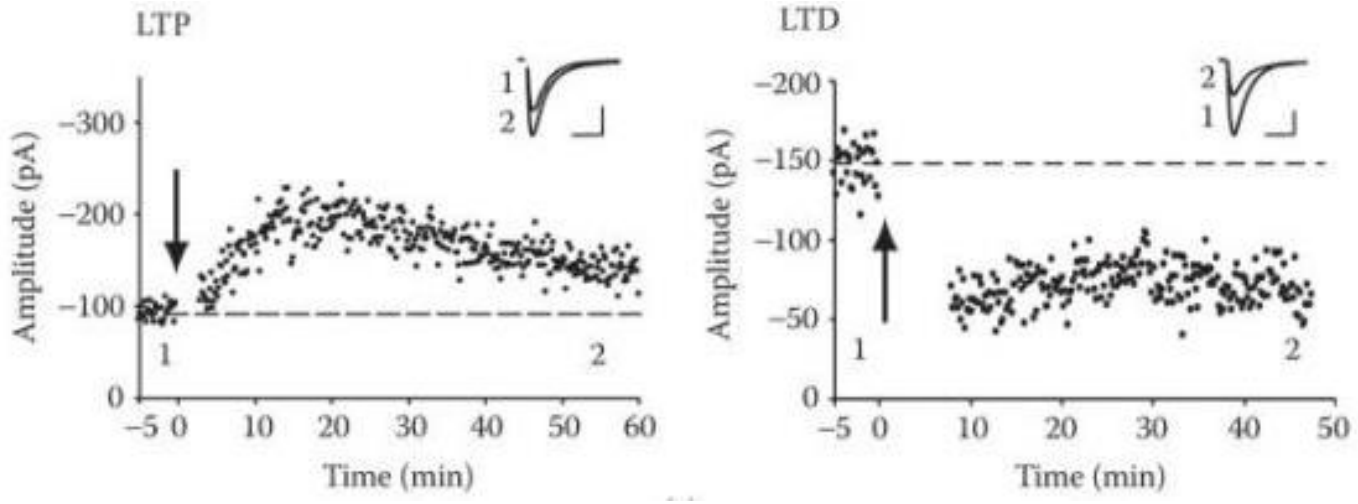
AMPA receptors are ionotropic glutamate receptors.

More glutamate receptors means stronger potentials in an active synapse.

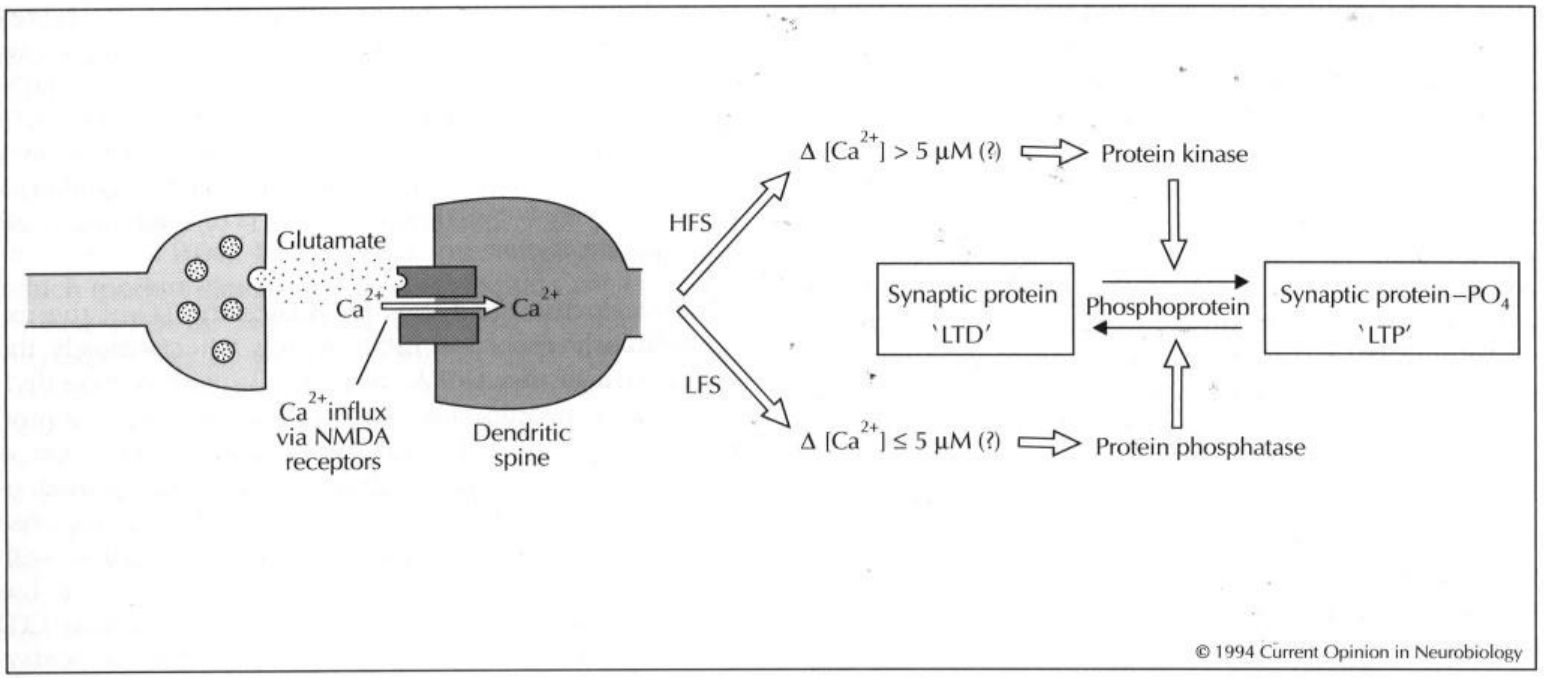
Fig. 19-11 - For LTP to last (Late LTP) the events of Fig. 19-10 must also lead to changes in protein synthesis and to formation of new synaptic connections.



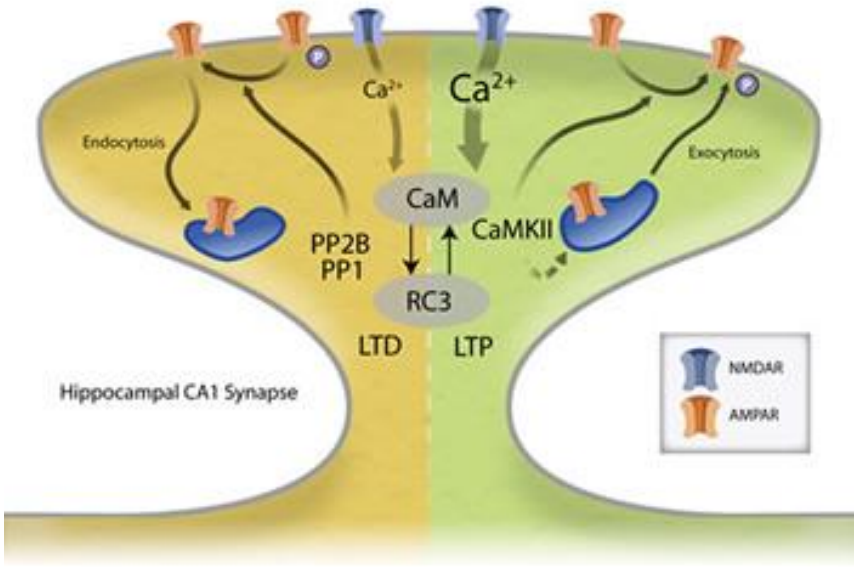
Long-term depression



If synapses simply continued to increase in strength as a result of LTP, eventually they would reach some level of maximum efficacy, making it difficult to encode new information. Thus, to make synaptic strengthening useful, other processes must selectively weaken specific sets of synapses. Long-term depression (LTD) is such a process. In the late 1970s, LTD was found to occur at the synapses between the Schaffer collaterals and the CA1 pyramidal cells in the hippocampus. http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=neurosci&part=A1729

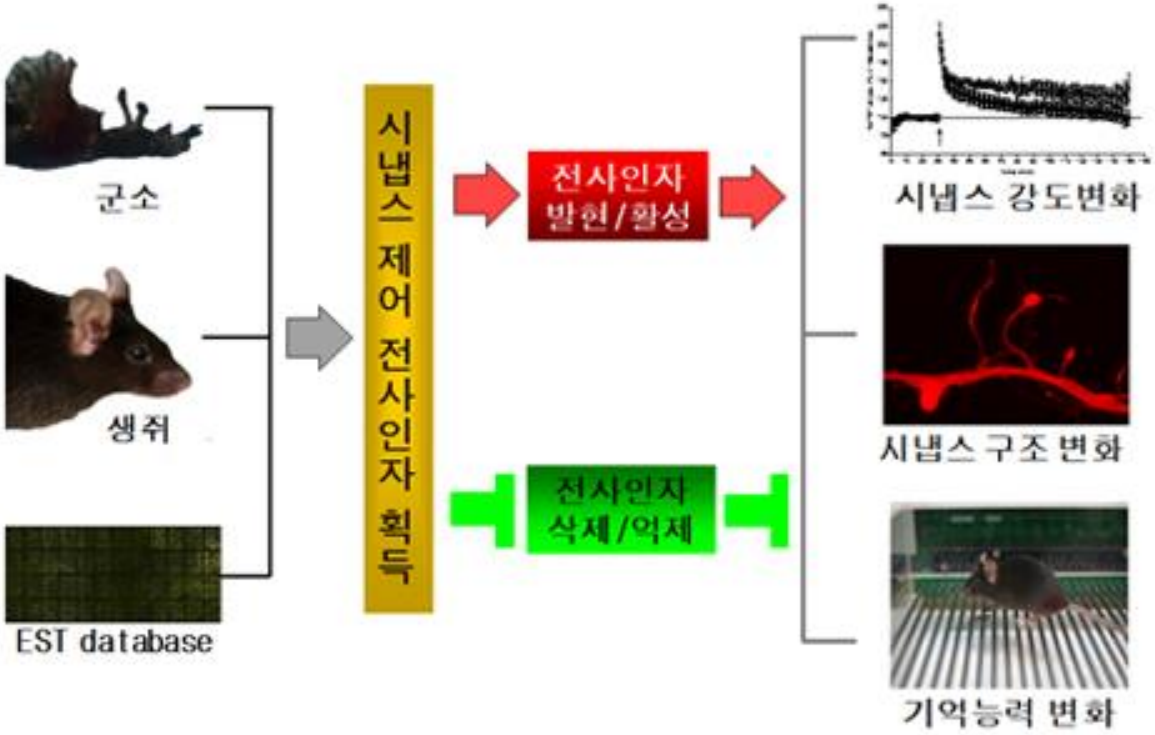


Whereas LTP at these synapses requires brief, high-frequency stimulation (HFS), LTD occurs when the Schaffer collaterals are stimulated at a low rate—about 1 Hz—for long periods (10–15 minutes). This pattern of activity depresses the EPSP for several hours and, like LTP, is specific to the activated synapses (Figure 25.12). Moreover, 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.



Long-term potentiation (LTP) and long-term depressions (LTD) at cortical synapses both require Ca2+ influx through NMDA receptors in the post synaptic cell and the activation of calmodulin (CaM). Importantly, other proteins at synapses (like RC3) can bind to CaM and alter its Ca2+-binding properties. Through unknown mechanisms, Ca2+/CaM then activate either CaM-dependent protein phosphatase (PP2B also known as calcineurin) or Ca2+/CaM-dependent protein kinase II (CaMKII). Depending on this choice, the synapse either gets weaker (LTD) or stronger (LTP). Once activated, PP2B and CaMKII can influence the physiological properties of the synapse by phosphorylating/dephosphorylating the AMPA subtype of glutamate receptors to change their properties or influence AMPA receptor number by affecting protein trafficking.
http://www.uth.tmc.edu/nba/resources/faculty/members/waxham.htm

- 1900's : Synapses as a site of learning is proposed.
- 1970's : Long-term synaptic plasticity is shown.
- 1980-2003 : Key molecular and genetic factors in synaptic plasticity are discovered. Link to learning behavior is demonstrated.
- Future : Bridging the gap between molecular neuroscience with systems/cognitive neuroscience.
- Therapeutic applications.



http://biosci.snu.ac.kr/professor/86/research.html?type=Details

Nature. 1999 Sep 2;401(6748):63-9.

Genetic enhancement of learning and memory in mice.

Tang YP, Shimizu E, Dube GR, Rampon C, Kerchner GA, Zhuo M, Liu G, Tsien JZ.
Department of Molecular Biology, Princeton University, New Jersey 08544-1014, USA.

Comment in:
Nature. 1999 Sep 2;401(6748):25-7.

Abstract

Hebb's rule (1949) states that learning and memory are based on modifications of synaptic strength among neurons that are simultaneously active. This implies that enhanced synaptic coincidence detection would lead to better learning and memory. If the NMDA (N-methyl-D-aspartate) receptor, a synaptic coincidence detector, acts as a graded switch for memory formation, enhanced signal detection by NMDA receptors should enhance learning and memory. Here we show that overexpression of NMDA receptor 2B (NR2B) in the forebrains of transgenic mice leads to enhanced activation of NMDA receptors, facilitating synaptic potentiation in response to stimulation at 10-100 Hz. These mice exhibit superior ability in learning and memory in various behavioural tasks, showing that NR2B is critical in gating the age-dependent threshold for plasticity and memory formation. NMDA-receptor-dependent modifications of synaptic efficacy, therefore, represent a unifying mechanism for associative learning and memory. Our results suggest that genetic enhancement of mental and cognitive attributes such as intelligence and memory in mammals is feasible.