

Synaptic mechanisms for long-term depression

Long-term potentiation in the hippocampus has been studied for over a decade, but the conditions for eliciting long-term depression have only recently been identified.

Neural networks that store information at synapses rely on mechanisms for increasing and decreasing synaptic strengths. In 1973 Bliss and Lømo reported that stimulating the perforant pathway projecting to the hippocampus with a high frequency tetanus resulted in a rapid and persistent elevation of the synaptic efficacy [1]. This form of long-term potentiation (LTP) lasts for many hours in slice preparations of the hippocampus and for many days *in vivo*. At some synapses in the hippocampus LTP can be induced by stimulating a test input only a few times if the stimulation is accompanied by strong postsynaptic depolarization [2,3]. An increase in synaptic efficacy under these conditions, as suggested by Hebb [4], is termed hebbian [5]. One of the most thoroughly explored uses of the simple hebb rule is in the formation of associations between patterns of neural activity [6]. Modifications of the simple hebb rule to include long-term depression of synaptic strength can improve the efficiency and performance of associative recall in neural network models [7,8].

Several types of depression have been studied in the hippocampus. Stimulating the perforant pathway at a sufficiently high frequency to induce LTP in the dentate gyrus can reduce the strength of a second pathway that is not stimulated or stimulated at a low frequency [9]. This form of synaptic depression is not as persistent as LTP. Relatively less work has been focussed on homosynaptic long-term depression (LTD), which is specific for the synapse that is activated and is an associative form of synaptic plasticity. Conditions for inducing homosynaptic LTD have recently been identified in the hippocampus [10] and neocortex [11]. Yet another form of LTD has been identified in the cerebellum [12]. This type of LTD has been called anti-hebbian as synaptic strengths are reduced rather than increased by coincident presynaptic and postsynaptic activity.

Network models of associative memory

In neural network models of associative memory, patterns of activity are stored by increasing the synaptic strengths between active neurons in the population [6]. More than one association can be stored in the same set of synapses using hebbian learning. But any learning system that uses a mechanism that can only increase the strengths of synapses will eventually degrade as all the synapses begin to saturate at their maximum values [13]. One way to prevent saturation of the synaptic strengths is to reduce them by non-specific decay but this results

in information loss at the same decay rate. This problem can be solved by using the covariance rule, an example of a variation on the hebb rule, which provides that the change in strength of a synapse should be proportional to the covariance between presynaptic and postsynaptic firing [7] (Fig. 1). The covariance rule achieves the optimal storage capacity for matrix-associative memories [8].

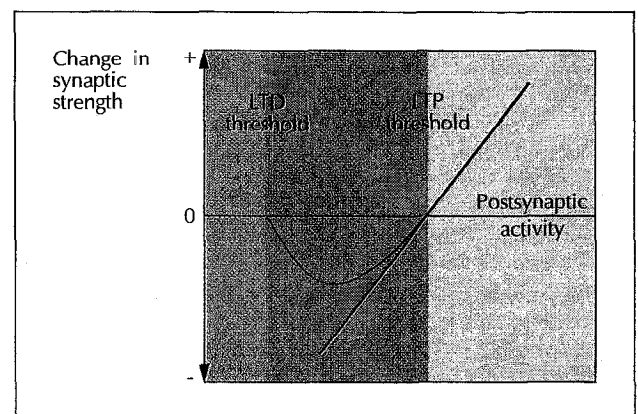


Fig. 1. Schematic drawing of the change in synaptic strength as a function of postsynaptic activity, for the BCM rule (red line) [14] and the covariance rule (black line) [7,13]. Both rules are variants of the hebb rule and postulate a threshold above which there is LTP (positive change in synaptic strength; grey shading) and below which there is LTD (negative change in synaptic strength; purple shading). In addition, the BCM rule has a threshold for LTD.

A network model of cortical development incorporating long-term depression as well as hebbian potentiation was proposed by Bienenstock, Cooper and Munro (BCM) [14]. As shown in Figure 1, the synapse is strengthened when the average postsynaptic activity exceeds a threshold and is weakened when the activity falls below the threshold level for potentiation, as in the covariance rule. But the BCM rule has an additional threshold that must be reached to produce depression. This threshold for depression gives the network model desirable stability properties.

Homosynaptic long-term depression in the hippocampus

Long-term depression of synapses in pyramidal neurons of hippocampus area CA1 can be induced when hyperpolarizing current is injected with intracellular microelectrodes while stimulating a synaptic input [10]. The membrane potential of the dendrite immediately adjacent to

the synapses is not known but the negative shift is probably smaller than in the cell body, where the current was injected, because of passive cable properties of the dendrite and the depolarization induced by the activation of other excitatory synapses. LTD can also be induced under more natural physiological conditions by pairing synaptic input between bursts of stimuli to another synaptic input [10]. This 'out-of-phase' stimulation of the postsynaptic neuron activates afterhyperpolarizing mechanisms and inhibitory interneurons. LTD is rapid in onset and lasts for over three hours in slice preparations. LTD has also been studied at synapses of pyramidal neurons in area CA3 [15].

The simultaneous depolarization of the postsynaptic membrane and activation of glutamate receptors of the N-methyl-D-aspartate (NMDA) subtype seems to be necessary for LTP induction [16]. The spread of current from conditioning synapses to test synapses in the dendritic tree could account for the ability of the conditioning pathway to produce associative potentiation of the test synapses. The NMDA receptor antagonist 2-amino-5-phosphonovaleric acid (AP5) blocks the induction of associative LTP in CA1 pyramidal neurons [17]. The application of AP5 to the bathing solution at the same concentration had no significant effect on associative LTD, which suggests that NMDA receptor activation is not necessary for the induction of LTD. Another glutamate analogue, 2-amino-3-phosphonopropionic acid (AP3), blocks LTD without affecting LTP [18]. AP3 blocks a metabotropic glutamate receptor of the quisqualate subtype that is linked with phosphoinositide hydrolysis [19]. The mechanisms for homosynaptic LTD may also be different from those underlying heterosynaptic LTD as the induction of heterosynaptic LTD in the dentate gyrus can be blocked by an NMDA receptor antagonist [20].

Homosynaptic long-term depression in the visual cortex

The visual response properties of neurons in the visual cortex of cats and monkeys can be modified by visual experience during the first few months of postnatal life, termed the critical period [21]. Normally, most cortical neurons respond to visual stimuli from either eye. Following deprivation of visual input to one eye by eyelid suture during the critical period, the ocular preference of neurons in primary visual cortex shifts toward the non-deprived eye. The loss of driving inputs from the closed eye during monocular deprivation could be mediated by synaptic depression based on a mechanism that reduced synaptic strengths when presynaptic activity was absent but postsynaptic activity was normal; conditions similar to those that produce heterosynaptic depression in the hippocampus. Recently, evidence for homosynaptic depression in visual cortex was found by infusion of muscimol, a γ -aminobutyric acid agonist, while one of the eyes was sutured closed during the critical period [22]. This procedure produced chronic hyperpolarization of neurons in a region around the site of infusion. When the eye was opened, neurons in visual cortex near the site of infusion could be driven only by the closed eye, in contrast to neurons more distant from the infusion site,

which could only be driven from the open eye. This observation could account for the changes observed in the receptive field properties of cells in adult cat visual cortex when visual experience is paired with iontophoretic depression of cellular activity [23].

Artola *et al.* [11] have identified a long-lasting synaptic depression in slices of rat neocortex. They report that depression was induced when a weakly depolarizing current was paired with a tetanizing input, but not when the membrane potential was below the threshold for depression. LTP occurred if the membrane potential was above a second threshold. This suggests that there is a narrow window of membrane potentials for eliciting depression. In addition, AP3 may block the induction of LTD in neocortical slices as it does in the hippocampus (A. Artola and W. Singer, personal communication). AP3 is also known to block glutamate-stimulated phosphoinositide hydrolysis in the rat neocortex during the critical period [24].

The evidence for homosynaptic depression in neocortex is consistent with the characteristics of LTD found in the hippocampus. The difference in the direction of current injection required to induce LTD could be due to differences between the resting potentials of neurons in neocortical slices, which are about 10–20 mV more negative than the resting potentials of CA1 hippocampal pyramidal neurons. This difference could shift the threshold for LTD relative to the resting potential. Thus, there could be a delicate balance that must be achieved between the number of excitatory synapses activated, the amount of current injected, and the change in the input resistance caused by the electrode leak to place the postsynaptic membrane potential in the window for inducing LTD. The same mechanism might also explain another report of homosynaptic depression [25], in which *in vivo* stimulation of the Schaffer collaterals in the hippocampus at 1–5 Hz sometimes produced a stable reversal of previously potentiated synapses in area CA1.

Conclusions

LTP in the hippocampus and neocortex has been very well studied during the last decade, but evidence for LTD has been reported only recently. The evidence summarized here that AP3 but not AP5 selectively blocks LTD suggests that the induction of LTD and LTP are caused by different receptors, but common intracellular mechanisms are still possible. Indeed, the same synapses in the hippocampus and neocortex could be repeatedly potentiated and depressed, which could be most economically explained if LTP and LTD both shared the same common set of regulatory mechanisms. Mechanisms that could account for LTD induction include voltage-sensitive regulation of intracellular levels of calcium [26,27] and phosphoinositide hydrolysis [19].

There seems to be a narrow window of postsynaptic membrane potentials that produce LTD when paired with synaptic input [11]. This suggests that cortical neurons store covariance information by finely adjusting den-

drift membrane potentials around the thresholds for LTD and LTP, which may themselves be regulated on a longer timescale. The significance of these mechanisms for learning and memory can be studied by incorporating them into network models of hippocampal circuitry [28].

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Terrence J. Sejnowski, Computational Neurobiology Laboratory, The Salk Institute, 10010 North Torrey Pines Road, La Jolla, California 92037, USA.