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Homosynaptic long-term depression in hippocampus and neocortex

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Computational models of self-organizing neural networks and associative memory depend on hebbian synaptic plasticity, a local learning rule for increasing synaptic strengths based on coincident electrical activity in presynaptic and postsynaptic neurons. Some forms of long-term potentiation (LTP) studied in the hippocampus and neocortex are hebbian. Learning rules in network models also incorporate long-lasting decreases in synaptic strengths for stability and efficiency. We review recent evidence for long-term depression (LTD) in the hippocampus and neocortex.

Key words: synaptic plasticity / long-term depression / long-term potentiation / glutamate receptor / metabotropic receptor / hippocampus / network models / associative memory

LONG-TERM potentiation[1] at some synapses in the hippocampus depends on coincident presynaptic and postsynaptic activity[2-5] (see also Teyler *et al*,[6] and Gustafsson and Wigström, this issue[7]). An increase in synaptic efficacy under these conditions, suggested by D. O. Hebb,[8] is termed hebbian[9,10] (see also McNaughton and Barnes, this issue[11]). One of the most thoroughly explored uses of the simple Hebb rule is in the formation of associations between patterns of neural activity.[12-19] The Hebb rule is appealing for this purpose because it provides a way of forming global associations between macroscopic patterns of activity in assemblies of neurons using only the local information available at individual synapses. However, modifications of the simple Hebb rule to include long-term depression can improve the efficiency and performance of associative recall in neural network models.[17,20]

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.[21-23] Such heterosynaptic depression of synaptic strengths can also be induced by low frequency stimulation (1-5 Hz).[24] These forms of synaptic depression are typically not as persistent as LTP. Relatively less work has been focused on homosynaptic long-term depression (LTD), which is specific for the synapse that is activated. Conditions for inducing homosynaptic LTD have recently been identified in the hippocampus[25] and neocortex[26] (Fregnac, Smith and Friedlander, personal communication; see also Teyler *et al*, this issue[6]). Homosynaptic LTD has also been identified in the cerebellum (Ito, this issue[27]). This type of LTD has been called anti-hebbian since synaptic strengths are reduced rather than increased by coincident presynaptic and postsynaptic activity.

In the first two sections of this review we focus on the evidence for homosynaptic LTD in the hippocampus and then in the neocortex. Although there are some differences, the similarity between the properties of LTD in these two preparations is striking, which suggests that there may be common underlying biochemical mechanisms. In the final section, we review the significance of LTP and LTD for models of associative memory in the hippocampus and the development of the visual cortex.

Homosynaptic long-term depression in the hippocampus

The stimulus paradigm that we used to produce either long-term depression or potentiation of synaptic strengths,[25] illustrated in Figure 1, is based on the finding that high frequency bursts (100 Hz) of stimuli spaced at 5 Hz are optimal in eliciting LTP.[28] This stimulus pattern is sometimes called a theta burst because it resembles the theta rhythm of the hippocampus. The theta burst introduces another important stimulus variable—the time interval between bursts. We were interested in studying the changes in synaptic strength of a separate input

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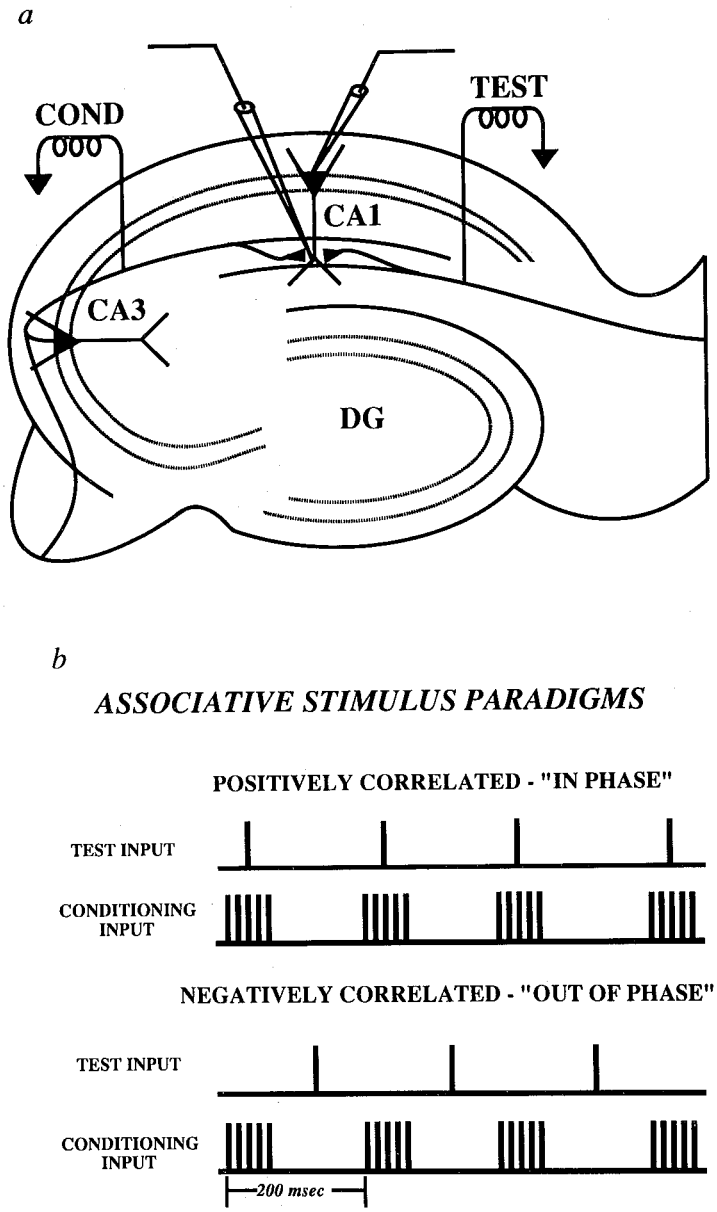

Figure 1. Hippocampal slice preparation and stimulus paradigms. a: Schematic diagram of the *in vitro* hippocampal slice showing recording sites in the CA1 pyramidal cell body (stratum pyramidale) and dendritic (stratum radiatum) layers, and two separate stimulus sites, TEST and conditioning (COND), activating Schaffer collateral and commissural afferents (see figure 1 in Gustafsson and Wigström, this issue,[7] for further anatomical details). b: Schematic diagram of stimulus paradigms used. Conditioning input stimuli were four trains of 100 Hz bursts. Each burst had five stimuli and the interburst interval was 200 ms. Each train lasted 2 s and had a total of 50 stimuli. Test input stimuli were four trains of shocks at 5 Hz frequency, each train lasting for 2 s. When these inputs were in phase, the test single shocks were superimposed on the middle of each burst of the conditioning input as shown. When the test input was out of phase, the single shocks were placed symmetrically between the bursts.

activated during the burst or during the interval between bursts. In a hippocampal slice preparation, we applied a theta burst as the conditioning stimulus to the Schaffer collaterals and a low-frequency test stimulus to a separate input on the opposite side of the recording site (Figure 1a); each shock of the test input was either superimposed on the middle of each burst of the conditioning input ('in-phase'), or occurred between the bursts ('out-of-phase') (Figure 1b).

Extracellular evoked field potentials were recorded from the apical dendritic and cell body layers of CA1 pyramidal cells. The 5 Hz test stimulus was first applied alone and did not itself induce long-lasting changes, as shown in Figure 2. When test and conditioning inputs were activated out-of-phase, we observed an associative long-term depression of the test input synapses (closed circles), accompanied by potentiation of the conditioning input (open circles). There was a marked reduction in the slope of the e.p.s.p. as well as a decrease in the amplitude of the population spike (not shown). The conditioning site was then stimulated alone, which elicited further potentiation of the conditioning pathway but did not significantly alter responses to the baseline stimulation of the test input (which was 1/10 s in this experiment, and as low as 1/15 min in other experiments). The testing pathway was not at its minimum since further depression could be elicited by additional out-of-phase stimulation. When test and conditioning inputs were activated in-phase, we observed long-term potentiation of both the test input synapses and the conditioning inputs, as shown in Figure 2 (in phase). Both the slope of the synaptic excitatory postsynaptic potential (e.p.s.p.) and population action potential (not shown) were significantly depressed for over 100 min following the induction of LTD.

Note that the stimulus patterns applied to each input in the above experiment (Figure 2) were identical in the in-phase and out-of-phase conditions, and only the relative phase of the test and conditioning stimuli was altered. With these stimulus patterns, synaptic strength could be repeatedly enhanced and depressed in a single slice. The duration of LTD in some slices lasted for over 180 min. We have varied the relative timing of the test pulse and have found that maximum depression results when the test

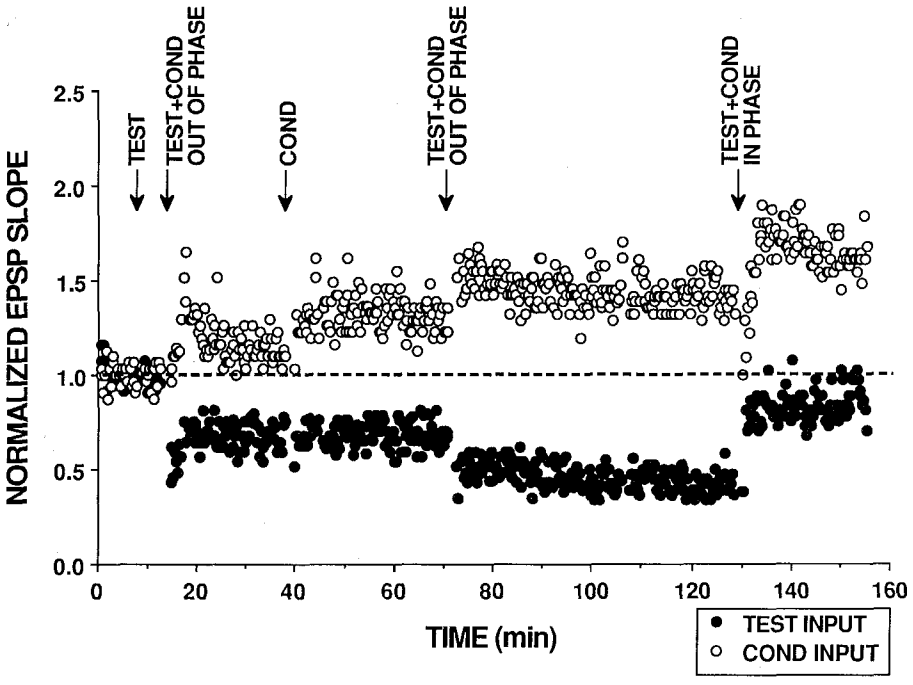

Figure 2. Illustration of associative long-term potentiation (LTP) and homosynaptic long-term depression (LTD) using extracellular recordings in hippocampal field CA1. A standard slice preparation was used and the slope of the field e.p.s.p. was measured and normalized to 1.0 during the stable baseline before stimulating the slice. The slope of the field e.p.s.p. of the test inputs (closed circles) could be potentiated or depressed depending on whether it was stimulated in phase or out of phase with the conditioning input (open circles) (see Figure 1).

pulse is approximately 20 ms after the end of each burst of the conditioning stimulus. In some experiments, the strength of a third unstimulated control input was tested and was not affected by any of these patterns of stimuli, indicating that the observed depression and potentiation is specific for the activated synapses and is not heterosynaptic.

The simultaneous depolarization of the postsynaptic membrane and activation of glutamate receptors of the N-methyl-D-aspartate (NMDA) subtype appears to be necessary for LTP induction[29-31] (see also Gustafsson and Wigström, and Malenka and Nicoll, this issue[7,32]). The spread of current from conditioning to test synapses in the dendritic tree probably accounts 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, 10 μM) blocks the induction of associative LTP in CA1 pyramidal neurons.[5,25,33] In contrast, the application of AP5 to the bathing solution at the same concentration had no significant effect on associative LTD (data not shown), which suggests that NMDA receptor activation is not necessary for the induction of LTD.

We have recently found that another glutamate analog, 2-amino-3-phosphonopropionic acid (AP3), blocks LTD without affecting LTP. AP3 is an antagonist of a metabotropic glutamate receptor that stimulates phosphoinositide (PI) hydrolysis in neurons.[34,35] When AP3 (25 μM) was present in the bathing solution, out-of-phase stimulation of the conditioning and test inputs in field CA1 did not produce a significant change in the e.p.s.p. slope or population spike (not shown), though in the same slice LTD could be elicited after AP3 was washed out (Figure 3). AP3 under the same conditions did not affect associative LTP. Thus, the induction of homosynaptic LTD seems to involve mechanisms different from associative LTP, including non-NMDA subtypes of glutamate receptors. The mechanisms for homosynaptic LTD may also be different from those underlying heterosynaptic LTD since the induction of heterosynaptic LTD in the dentate gyrus can be blocked by an NMDA receptor antagonist (Desmond, Colbert, Zhang and Levy, personal communication).

The theta burst conditioning stimulus activates inhibitory neurons as well as pyramidal cells, though the balance may be different *in vitro* and *in vivo*. Thus, a test shock that is out-of-phase with a conditioning stimulus arrives when the postsynaptic neuron is hyperpolarized as a consequence of inhibitory postsynaptic potentials and after hyperpolarization from mechanisms intrinsic to pyramidal neurons.

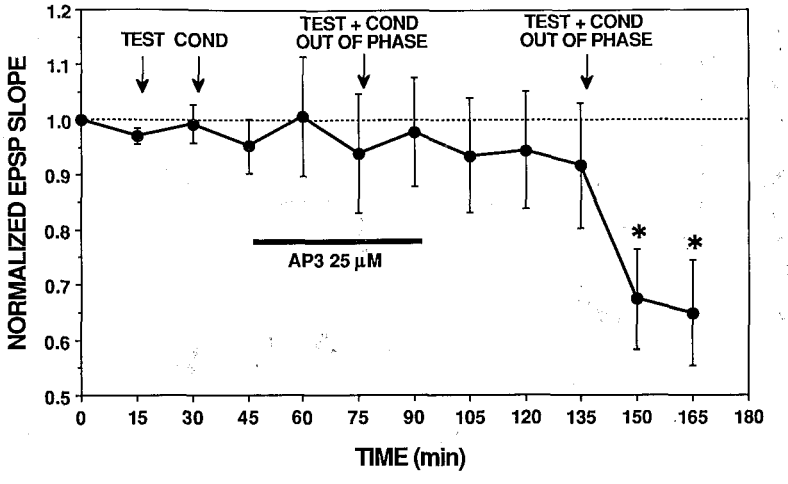

Figure 3. The glutamate analog 2-amino-3-phosphonopropionic acid (AP3) blocks homosynaptic LTD elicited by out-of-phase stimulation of synapses on hippocampal neurons in area CA1. The results from 7 experiments have been normalized and averaged. The time course of the average e.p.s.p. slope showed no change following out-of-phase pairing of the test and conditioning pathways in the presence of AP3 but the same pattern of stimulation elicited significant decrease following washout of AP3. The test and conditioning stimuli by themselves did not produce any change. (*$P<0.05$ paired t-test compared to prestimulation baseline)

This suggests that LTD may occur when presynaptic activation is coupled with less postsynaptic depolarization than the stimulus would have otherwise produced. To test this hypothesis, we injected current with intracellular microelectrodes to hyperpolarize or depolarize the cell body of a CA1 pyramidal neuron while stimulating a synaptic input at 5 Hz. Pairing the injection of depolarizing current with the test input led to LTP of those synapses, while a control input inactive during the stimulation did not change, as reported previously.[3-5]

When prolonged injection of hyperpolarizing current was paired with the same 5 Hz test stimuli, LTD was induced in the activated pathway but not at unstimulated synapses.[25] It is important to note that the application of either depolarizing current, hyperpolarizing current, or the test synaptic stimulation alone did not induce long-term alterations in synaptic strength. The membrane potential of the dendrite immediately adjacent to the synapses was not known, but the negative shift was probably smaller than in the cell body, where the current was injected, because of passive cable properties of the dendrite and the depolarization and conductance increase induced by the activation of other excitatory synapses. The relationship between LTD induced by theta bursts and by pairing current injection with low frequency stimulation is uncertain; however, in recent experiments (Stanton, Chattarji and Sejnowski, unpublished) we have found that AP3 also blocks LTD induced by current injection, which suggests that the same non-NMDA glutamate receptors are involved.

Our original report of homosynaptic LTD in the hippocampus was for pyramidal neurons in area CA1. We have subsequently studied synapses on pyramidal neurons in area CA3.[36] Interestingly, mossy fiber synapses, which exhibit a non-NMDA mediated form of LTP,[37,38] do not exhibit homosynaptic LTD. The mossy fibers, however, can serve as the conditioning input for inducing LTD in associational and commissural synapses on the same dendrites of CA3 pyramidal cells. We have also obtained LTD in CA1 pyramidal neurons when the theta burst conditioning input was antidromic rather than orthodromic, suggesting that the primary influence of the theta burst stimulation is through the membrane potential (Jester and Sejnowski, in preparation).

Homosynaptic long-term depression in the visual cortex

Long-term depression of synaptic strength has also been observed in other areas of the brain (see Ito *et al*, this issue[27]). However, homosynaptic depression similar to that found in the hippocampus has thus far only been reported in the neocortex. 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, a time interval termed the critical period.[39] 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. In another type of experiment, a misalignment of the two eyes during the critical period produces neurons that respond to only one eye and, as a consequence, binocular depth perception is impaired.[40]

These and many other experiments have led to testable hypotheses for the mechanisms underlying synaptic plasticity during the critical period.[41] Voltage-dependent entry of calcium into spines and the dendrites of postsynaptic cells in visual cortex may trigger the molecular changes required for synaptic modification during the critical period. Infusion of the NMDA receptor antagonist AP5 into visual cortex does indeed block the shift in ocular dominance normally associated with monocular deprivation.[42] However, activation of the NMDA receptor in the visual cortex is required to produce normal visual responses, so that a definitive test of this hypothesis may be difficult to make (DeFreitas and Stryker, personal communication).

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 is absent but postsynaptic activity is normal.[43] This is similar to the conditions that produce heterosynaptic depression in the hippocampus. Recently, evidence for homosynaptic depression in visual cortex was found by infusion of muscimol, a GABA agonist, while one of the eyes was sutured closed during the critical period.[44] 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. One interpretation of these results is that presynaptic transmitter release onto hyperpolarized cells leads to a long-term depression of the input synapses arising from the lateral geniculate nucleus but that inactive terminals

are not affected. This is similar to the conditions that we found produce homosynaptic LTD in the hippocampus.

The receptive field properties of cells in cat visual cortex can be altered even in the adult by visual experience paired with iontophoretic excitation or depression of cellular activity.[44,45] Two groups have recently provided direct evidence for homosynaptic depression in neocortex (see also Teyler *et al*, this issue[6]). In slices of visual cortex from cats, hyperpolarizing current injected into pyramidal neurons paired with low-frequency stimulation of white matter resulted in a transient depression of synaptic strength, whereas pairing the same stimulation with depolarizing current resulted in long-lasting potentiation of the synapse (Fregnac, Smith and Friedlander, personal communication). Artola *et al*[26] have identified a longer-lasting depression under somewhat different conditions 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 a hyperpolarizing input was paired. This suggests that there is a narrow window of membrane potentials for eliciting depression: there is no long-term change in synaptic strength if the membrane potential is below the threshold for depression, and LTP occurs if the membrane potential is above a second threshold. 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 turnover in the rat neocortex,[46] which inspired us to use AP3 to block LTD in the hippocampus (Stanton, Chattarji and Sejnowski, unpublished).

The evidence for homosynaptic depression in neocortex is consistent with the characteristics of LTD that we have 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. The threshold for LTD found in the neocortex may explain why some groups have been unable to repeat the conditions that we have found to be effective in eliciting LTD in the hippocampus.[47,48] 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 effectiveness of the out-of-phase stimulus that we used to obtain LTD might similarly depend on the strength of the test input relative to the strength of the inhibition elicited by the conditioning input. We are exploring these possibilities. The same explanation might also explain another report of homosynaptic depression,[49] in which *in vivo* stimulation of the Schaffer collaterals at 1-5 Hz sometimes produced a stable reversal of previously potentiated synapses in area CA1. Such low frequency stimulation could mimic other conditions that elicit homosynaptic LTD in neocortical[26] and hippocampal slices.[25]

Possible mechanisms underlying homosynaptic LTD

The evidence reported here that AP3 but not AP5 selectively blocks LTD suggests that the induction of LTD and LTP are caused by different receptor mechanisms, but common intracellular mechanisms are still possible. Indeed, we observed that the same synapses can be repeatedly potentiated and depressed, which can be parsimoniously explained if LTP and LTD both share a common set of regulatory mechanisms. A related issue is whether sufficiently strong synaptic depression can entirely abolish the e.p.s.p. This has never been observed. Thus, it may be possible that only a previously potentiated synapse can be depressed. Further experiments are needed to settle these issues.

One mechanism that is apparently not sufficient to account for homosynaptic LTD is the absence of NMDA-gated calcium influx during stimulation. When NMDA receptors are blocked with AP5, which should block calcium entry through NMDA receptors, stimulation of synapses does not lead to LTD (see Goldman *et al*[50]). This does not, of course, rule out the possibility that LTD is produced by the absence of calcium coupled with some other factor. For example, LTD can be induced in neocortical neurons that have been injected with EGTA.[51] Lisman[52] has suggested that the necessary condition for inducing LTD may be an intermediate elevation of calcium, rather than a minimal or maximal elevation, coupled with synaptic activity. This possibility could be tested by direct measurement of intracellular calcium levels in the dendrites of

pyramidal neurons using calcium-sensitive dyes. Other mechanisms that could account for the voltage sensitivity of LTD induction are equally possible, such as voltage-sensitive mechanisms for glutamate-stimulated PI turnover.

Network models based on LTP and LTD

Neural network models of associative memory are sometimes called matrix memories because the modifiable synapses between neurons in a population form a matrix and patterns of activity are stored by increasing the weights between active neurons in the population. More than one association can be stored in the same matrix, so long as the input vectors are not too similar to each other. This model of associative storage is simple and has several attractive features: first, the learning occurs in only one trial; second, the information is distributed over many synapses, so that recall is relatively immune to noise or damage; and third, input patterns similar to stored inputs will give outputs similar to the stored outputs, a form of generalization.

The matrix model also has some limitations: first, items with input vectors that are similar, that is, with subpopulations of activated neurons having a significant overlap, will produce outputs that are mixtures of the stored outputs; but discriminations must often be made among similar inputs. Second, the matrix model of associative memory cannot respond contingently to pairs of inputs, that is, have an output that is other than the sum of the individual outputs. Lastly, 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.[53] LTD may be a way of solving some of these difficulties.

One way to prevent saturation of the synaptic strengths is to reduce the weights by nonspecific 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[17] (see Figure 4). The covariance rule achieves the optimal storage capacity for matrix associative memories.[20]

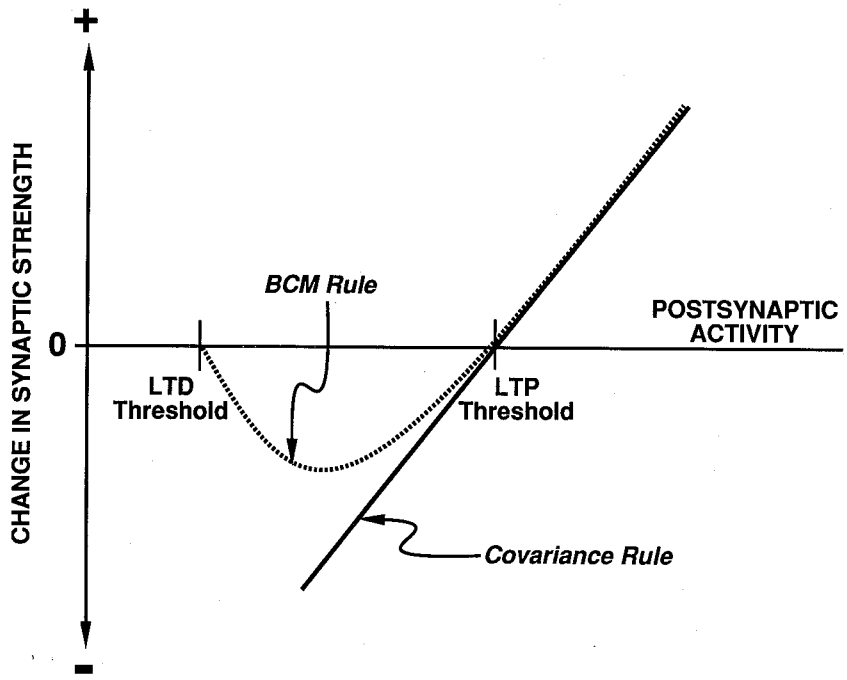

Figure 4. Schematic drawing of the change in synaptic strength as a function of the postsynaptic activity for the BCM rule (dotted line)[56] and the covariance rule (solid line).[17,53] Both rules are variants of the Hebb rule and postulate a threshold above which there is LTP (positive change in synaptic strength) and below which there is LTD (negative change in synaptic strength). In addition, the BCM rule has a threshold for LTD.

Thus, the strength of a synapse should increase if the firing of the presynaptic and postsynaptic elements are positively correlated, should decrease if they are negatively correlated and should remain unchanged if they are uncorrelated. Both heterosynaptic depression and homosynaptic depression are required by the covariance rule but performance almost as good can be obtained by using only one or the other.[20] However, homosynaptic LTD, by preserving synaptic specificity, should be more sensitive to higher-order correlations in synaptic activity than heterosynaptic LTD.

Hebbian synaptic plasticity has been used to model the development of ocular dominance and orientation columns in visual cortex.[54,55] A network model of cortical development incorporating long-term depression as well as hebbian potentiation was proposed by Bienenstock, Cooper and Munro.[56] Their model of synaptic plasticity, now known as the BCM rule (Figure 4), strengthens the synapse when the average postsynaptic activity exceeds a threshold and weakens the synapse 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 (Figure 4), as is found in neocortex.[26] This threshold for depression gives the network model desirable stability properties.

The experiments on long-term depression in the hippocampus summarized in this chapter were inspired by ideas that first arose in the context of modeling associative memory. The covariance learning rule identified anti-correlation as the critical condition for inducing synaptic depression. Simplifying models provide a general framework for thinking about the relationships that could exist between signals in complex circuits, like those found in the hippocampus and neocortex, but it is also necessary to incorporate realistic details into the model to make specific predictions.[57]

Summary

Finding evidence for homosynaptic LTD in the brain is an important first step but we are still a long way from understanding its significance. More needs to be known about the timing relationships that produce these phenomena, as well as the spatial integration of synaptic signals within dendritic trees. The conditions for eliciting homosynaptic LTD are more delicate than those for inducing LTP, perhaps because the range of postsynaptic membrane potentials that elicit LTD is relatively narrow.[26] This suggests that cortical structures store covariance information by finely regulating dendritic membrane potentials around the thresholds for LTD and LTP. Unfortunately, it is not possible at present to explore these possibilities by measuring or controlling accurately dendritic potentials in cortical neurons. Models of dendritic processing may be needed to sharpen our intuitions and help us to interpret other experimental results.[58]

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