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LTD, LTP, and the Sliding Threshold for Long-Term Synaptic Plasticity

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INTRODUCTION

Long-term potentiation (LTP) is a long-lasting increase in synaptic strength which has attracted a great deal of interest as a possible synaptic mechanism of both learning and memory, and experience-dependent development of cortical circuitry. More recently, long-term depression (LTD) of synaptic efficacy has also been demonstrated in both the hippocampus and a growing list of neocortical areas. In this chapter, I will review the literature on stimulus conditions that have been found to elicit LTD, and describe cellular mechanisms by which the threshold of synaptic activity necessary to induce LTP versus LTD is dynamically regulated in a way that is essential to the functional roles of these forms of synaptic plasticity.

The properties of induction of LTP are strikingly similar to the theoretical "Hebb synapse" (Hebb, 1947) where, if synaptic strength is increased when presynaptic activity coincides with postsynaptic excitation, those synapses will be more likely to be activated upon subsequent presentations of similar input patterns. The persistence of LTP (months or longer), its observation at an ever-widening number of cortical and subcortical synapses, and the ability of pharmacological agents that block LTP induction to impair learning acquisition and developmental plasticity, are all consistent with the idea that LTP may play a role in both activity-driven development of cortical networks and adult memory storage (for review, see Bliss and Collingridge, 1993; Fox and Daw, 1993).

More recently, there has been a similar explosion of interest in cellular mechanisms that lead to LTD of synaptic strength. There are good reasons to suspect such mechanisms exist. For one, if there is an upper limit to the amount of LTP that can be elicited, then some mechanism for preventing saturation of all synapses in a maximally potentiated state would be necessary. Second, an "anti-hebbian" form of LTD, in which presynaptic activity that is unable to cause postsynaptic excitation depresses synaptic strength, could serve to improve the signal-to-noise ratio of sensory input activation of stored memories, by maximizing the separation of synaptic strengths. However, as will be suggested below, the interaction of mechanisms for LTP and LTD of synaptic strength with time-variant conductances also confers on neurons the ability to compute and store a covariance function between converging neuronal inputs. The forms and properties of LTD expressed, physiological patterns of stimulation that induce LTD, and neurochemistry of induction and maintenance are all areas of expanding research.

HETEROSYNAPTIC LTD

In the history of the study of long-term synaptic plasticity, there have been a number of experiments suggesting the mechanisms for increasing and decreasing synaptic strength are interrelated. The earliest experimental studies described a heterosynaptic LTD of synaptic strength that occurred at one set of synapses when LTP was induced in a second input synapsing on the same neurons. Heterosynaptic LTD appears to be exhibited by a number of synapses, including Schaffer collateral-CA1 synapses (Lynch et al., 1977), perforant path synapses in the dentate gyrus (Levy and Steward, 1979, 1983), and commissural/associational synapses in field CA3 (Bradler and Barrionuevo, 1990). In all these cases, it appeared that LTD was a non-selective depression of inactive inputs linked to the generation of homosynaptic LTP by high-frequency stimulation.

There have been studies addressing the cellular mechanisms underlying the induction of heterosynaptic LTD. For example, studies have shown that heterosynaptic LTD is facilitated by the blockade of inhibition (Abraham and Wickens, 1991), that activation of L-type voltage-dependent calcium channels can be necessary to induce heterosynaptic LTD (Wickens and Abraham,

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1991; Christie and Abraham, 1994), and that changes in early gene expression are associated with the persistence of this form of LTD (Abraham et al., 1994). However, the fact that, to elicit heterosynaptic LTD, LTP also has to be induced has made it impossible to study this form of LTD in isolation.

ASSOCIATIVE LTD AND COMPUTATION OF COVARIANCE

Recently, a number of studies have described new stimulus paradigms for eliciting homosynaptic LTD. An associative homosynaptic form of LTD can be elicited by temporally mismatching stimulation of two inputs that converge on the same neuron (Frégnac et al., 1988; Stanton and Sejnowski, 1989; Chattarji et al., 1989), or mismatching presynaptic and postsynaptic activation (Debanne et al., 1994). In these studies, the mismatching of the phase of two patterns of repetitive stimulation appeared to produce a condition where presynaptic activity on one of the input lines was paired with postsynaptic hyperpolarization that suppressed firing.

There has also been a report of a failure to evoke LTD (Paulsen et al., 1993) using an out of phase stimulus paradigm identical to ours (Stanton and Sejnowski, 1989). Interestingly, Christie and Abraham (1992) reported a similar failure in the dentate gyrus, but went on to find that prior low-frequency stimulation could "prime" a pathway to successfully exhibit associative LTD where it previously had not. However, Kerr and Abraham (1993) unsuccessfully attempted a similar priming in hippocampal field CA1, but could not evoke associative LTD in this way. It is important to point out that, as a control for the experiments we conducted in our initial reports in field CA1 (Stanton and Sejnowski, 1989; Chattarji et al., 1989), we always applied a low-frequency stimulation alone prior to out of phase conditioning, to establish that this was not sufficient to evoke LTD. In the hypothesized mechanism modulating threshold for induction of synaptic plasticity I will outline below, the failure or success of out of phase stimulation should depend critically on both the previous history of synaptic activity and the relation of synaptic activity to membrane potential.

In confirmation of the conditions necessary to produce associative LTD, it has also been evoked directly in field CA1 of the hippocampus by pairing postsynaptic hyperpolarization (accomplished by intracellular current injection, synaptically, evoked inhibitory postsynaptic potentials (i.p.s.p.s) or direct application of GABA) with presynaptic stimulation (Stanton and Sejnowski, 1989; Thiels et al., 1994; Yang et al., 1994). In visual cortex, LTD has been variously reported following stimulation paired with either weak depolarization (Artola et al., 1990) or hyperpolarizing current injection (Frégnac et al., 1994). It is important to note that the typical resting membrane potential of hippocampal pyramidal neurons (−60 to −65 mV) is significantly more positive than pyramidal neurons in visual cortex (−70 to −80 mV). The preponderance of evidence is now clear: LTD is induced by the pairing of presynaptic activity with a postsynaptic membrane potential that is hyperpolarized *relative to that necessary for induction of LTP.* However, as I will discuss below, there is a good reason to believe that the amplitude of activity and membrane potential necessary to elicit LTD is not a fixed quantity.

The form of associative LTD described above has some very important mathematical implications. This LTD can most simply be described as a "pre not post" condition, which is the converse of the hebbian coincidence detection necessary to induce associative LTP ("pre and post"; Gustaffson et al., 1987). However, since both depolarizing and hyperpolarizing postsynaptic conductances have characteristic peak and decay time constants, the arrival of any excitatory input triggers a sequence of conductance changes, both excitatory postsynaptic potentials (e.p.s.p.s) and feed-forward and recurrent i.p.s.p.s, which will ensure that subsequent inputs will be more likely to induce either LTP or LTD, depending on their exact timing of arrival. Thus, the associative nature of both LTP and LTD, depending, in part, on postsynaptic membrane potential, confers on neurons the ability to compute a covariance function between converging inputs and store the result.

Theoretical studies have indicated that neurons that can compute and store a covariance function can optimize storage in a matrix memory (Sejnowski, 1977; Wilshaw and Dayan, 1990). However, it is not yet clear what function such a computation serves for hippocampal processing or long-term cortical memory storage. I emphasize that covariance depends on both temporal frequency and phase. The hippocampus can exhibit coordinated neuronal oscillations (5–7 Hz theta rhythm) and Winson and colleagues showed some time ago (1988) that synaptic inputs that are phase-locked with these oscillations can preferentially elicit LTP. It is intriguing to think that, if particular subpopulations of hippocampal neurons can be driven in phase-locked oscillations, and if they coherently drive their cortical targets, this hippocampal-cortical group might represent the neural substrate of coherent "binding" of a sensory experience, which would then be stored by the in and out of phase computation of covariant signals riding on these carrier waves. Furthermore, many such groups could be active, with differing frequency and phase, permitting the hippocampus to guide multiplexing and storage of separately bound engrams throughout cortex. Understanding the rules governing the induction of LTP and LTD by such interacting stimuli will be essential to eventually testing this hypothesis.

LOW-FREQUENCY SYNAPTIC ACTIVITY INDUCES HOMOSYNAPTIC LTD

Recent work has identified patterns of input activity that can elicit homosynaptic LTD without the application of any LTP-inducing stimulation. Consistent with the hypothesis that LTD should result from presynaptic glutamate release that is unable to produce strong postsynaptic depolarization, sustained low-frequency synaptic stimulation (LFS; typically 1–5 Hz/10–15 min) has been found to elicit homosynaptic LTD at Schaffer collateral-CA1 synapses in the hippocampus (Dudek and Bear, 1992;

Mulkey and Malenka, 1992; Wexler and Stanton, 1993). While some of these studies found that LFS was effective at eliciting LTD at naive, previously unstimulated synapses, earlier work suggested that LFS is much more effective at causing "depotentiation" LTD at synapses where LTP has been recently induced (Barrionuevo et al., 1980; Stäubli and Lynch, 1990; Fujii et al., 1991; Wexler and Stanton, 1993). This suggests that the cellular mechanisms for the induction of LTP and LTD are functionally related, and that the previous history of synaptic activity and plasticity can modify their gain.

THE "SLIDING THRESHOLD" FOR LTP AND LTD

There have been many computational modeling studies of neuronal plasticity algorithms and their possible roles in both the activity-driven development of neural circuits and the storage of memories. While many utilized rules that do not have obvious correlates in neurophysiology, the ones that attempted to implement more physiological synaptic rules typically began with something much like a hebbian synapse. However, they often encountered the problem that, when correlated pre- and postsynaptic activation led to the induction of persistent increases in connection strength, this also increased the probability for further correlations to cause greater increases, until all the connections in the network were saturated at their maximum and stored information was lost. Therefore, some mechanism for inducing LTD of connection strength was often incorporated, in which either a "pre not post" or "post not pre" rule led to LTD. However, with LTD as a counterbalance to LTP, the difficulty was now merely translated into half of the synaptic connections potentiating to saturation, while the other half depressed to a minima.

Bienenstock, Cooper, and Munro (1982) encountered this problem in modeling the development of visual cortex, and identified an effective solution, namely, incorporating a "sliding threshold" for the induction of both LTP and LTD, as illustrated in Figure 1. In their model (BCM), a previous history of high levels of synaptic activation produced a rightward-shift in threshold (θ_m) that made it less likely for input to elicit LTP and more likely to evoke LTD. Conversely, low levels of activation caused a leftward-shift in threshold that favored the induction of LTP. In this way, model neurons maintained their connection strength within the linear range, which maximized information storage in the network and allowed it to develop activity-driven, stable ocular dominance-type columns. This idea suggested that LTD may be an essential component of synaptic plasticity, and also that some kind of link between the mechanisms for LTP and LTD may be necessary for their threshold to be co-regulated. However, there was no experimental support for this hypothesis.

New experimental data do support the idea that the synaptic plasticity threshold is variable, and that LTP and LTD are dynamically regulated in a manner very similar to these theoretical predictions. In studies of LTP, Huang et al. (1992) showed that application of brief high-frequency bursts of stimuli that were sufficient to elicit short-term potentiation (STP), but not LTP, also *suppressed* the later induction of LTP at Schaffer collateral-CA1 synapses, while not suppressing the induction of LTP at control, unstimulated synapses on the same neuron. Moreover, we have found that similar STP-inducing stimuli *enhanced* the amount of LTD elicited by LFS in field CA1 (Wexler and Stanton, 1993), and, as mentioned previously, Christie and Abraham (1994) reported that theta frequency (5 Hz) stimulation can also enhance the amount of associative LTD elicited in the dentate gyrus. Taken together, these studies support the idea of a "sliding threshold" for plasticity, at least for the case in which higher levels of previous synaptic activity can shift those synapses to favor induction of LTD and suppress LTP. It should be noted that the activity necessary to shift the LTP/LTD threshold does not, itself, need to cause long-term changes in synaptic strength.

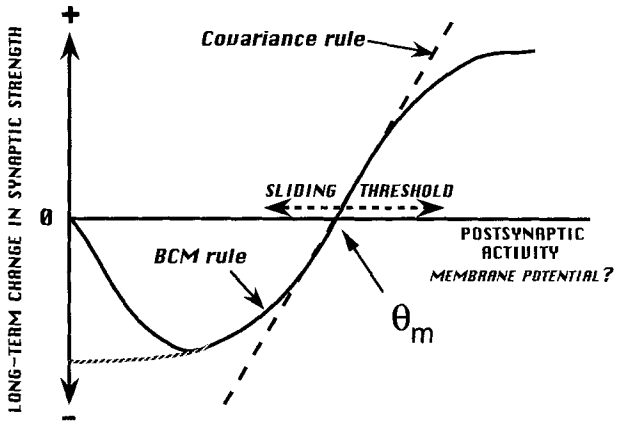

FIGURE 1. "Sliding threshold" function for bidirectional modification of synaptic strength. The theoretical learning rule of Bienenstock et al. (1982) is plotted as a solid line (BCM rule), compared to a simple covariance function (dotted line) and a modification rule that does not return to the origin at zero postsynaptic activity (hatched line). θ_m is the crossover threshold from LTD to LTP induction, and it is this crossover point that "slides" as a function of previous synaptic activity. (Reprinted from Wexler and Stanton, 1993.)

GLUTAMATE RECEPTORS AND THE INDUCTION OF LTD

There have been a number of investigations into the requirement for particular glutamate receptor subtypes necessary for the induction of LTD. While our earliest studies indicated that the induction of associative LTD by pairing presynaptic stimulation with postsynaptic hyperpolarization was *not* blocked by an N-methyl-D-aspartate (NMDA) receptor antagonist (Stanton and Sejnowski, 1989), we (Wexler and Stanton, 1993) and others (Dudek and Bear, 1992; Mulkey and Malenka, 1992) have found that the induction of LFS LTD can be prevented by NMDA receptor blockers, while Desmond et al. (1991) reported similar findings for the induction of heterosynaptic LTD in vivo. However, we also observed that high frequency stimulation ap-

plied during NMDA receptor blockade can be effective in eliciting LTD in field CA1 of slices from immature animals (Velišek et al., 1993), suggesting that there is not an absolute requirement for NMDA receptor activation to evoke LTD under all conditions.

We have also performed experiments indicating a requirement for activation of metabotropic glutamate receptors to induce LTD (Stanton et al., 1991), a finding replicated by others in hippocampus (Bashir et al., 1993) and visual cortex (Kato, 1993). Our study employed the antagonist (2-amino-3-phosphonopropionic acid (AP3), which is somewhat selective for metabotropic receptors coupled to phospholipase C, while the others used the more broad spectrum antagonist (RS)-alpha-methyl-4-carboxyphenylglycine (MCPG). In contrast, Xiao et al. (1995) were unable to block depotentiation in hippocampus with MCPG. While the lack of pharmacological antagonists selective for particular metabotropic receptor subtypes hampers the dissection of their roles in LTD, it seems likely that the activation of both NMDA and metabotropic glutamate receptors, as well as, perhaps, voltage-dependent Ca^{2+} channels (Wickens and Abraham, 1991; Christie and Abraham, 1994), can all contribute to the induction of LTD at cortical synapses. This may simply be by virtue of their ability to cause increases in intracellular [Ca^{2+}] within a window necessary for LTD, or could also reflect the involvement of other second messenger systems regulated by metabotropic receptors.

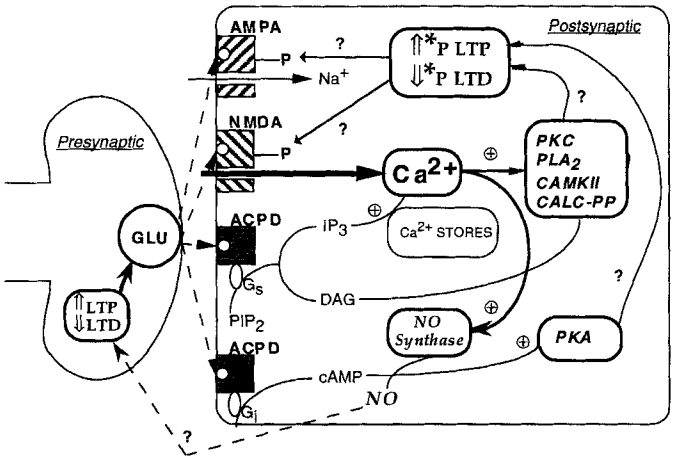

FIGURE 2. Schematic of some intracellular messenger cascades that have been suggested to play a role in the induction of LTD, and/or in biasing synapses in favor of either LTP or LTD. Abbreviations: ACPD = metabotropic receptors; cAMP = cyclic adenosine 3′,5′-monophosphate; AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate receptors; CALC/PP1 = Ca^{2+}/calmodulin dependent protein phosphatase calcineurin; CAMKII = Ca2+/calmodulin-dependent protein kinase II; DAG = diacylglycerol; G_i = inhibitory g-protein; GLU = glutamate; G_s = stimulatory g-protein; IP_3 = inositol triphosphate; LTP = long-term potentiation; LTD = long-term depression; NMDA = N-methyl-D-aspartate; NO = nitric oxide; PKC = Ca^{2+}/phospholipid-dependent protein kinase; PLA_2 = Ca^{2+}-dependent phospholipase A_2; PIP_2 = phosphatidylinositol 4,5-bisphosphate; *P = phosphorylation site.

INTRACELLULAR MESSENGERS, LTD, AND DYNAMIC REGULATION OF PLASTICITY THRESHOLD

Given the recency of interest in LTD, there is little known about the cellular mechanisms that induce or maintain LTD. However, work has begun to suggest that some of the messenger and enzyme cascades that have been implicated in the induction of LTP may also contribute to LTD, as summarized schematically in Figure 2. For example, many studies indicate that an increase in postsynaptic [Ca^{2+}], probably to levels *below* those necessary to induce LTP, is one necessary condition to induce LTD. Injection of a Ca^{2+} chelator into visual cortical neurons converts stimuli which normally induce LTP to evoke LTD (Kimura et al., 1990; Brocher et al., 1992), while chelating Ca^{2+} in CA1 pyramidal neurons blocks the induction of LTD by LFS (Mulkey and Malenka, 1992). In the immature hippocampus, blocking NMDA receptors (Velišek et al., 1993) causes a stimulus which normally evokes LTP to elicit LTD instead. Interestingly, while elevating extracellular [Ca^{2+}] in the hippocampus can cause LTP (Turner et al., 1982), Artola et al. (1996) have recently found that a similar manipulation causes LTD in neocortex, which they suggest is due to the relative hyperpolarization of neocortical, compared to hippocampal, pyramidal neurons. These findings lead to the suggestion that a lower magnitude of postsynaptic calcium influx may trigger a different population of calcium-mediated processes than the larger influx necessary for LTP.

We have recently completed experiments addressing the source(s) of Ca^{2+} necessary for the induction of LTD. Using a number of different pharmacological agents that deplete postsynaptic intracellular stores of Ca^{2+}, we found that such depletion blocked the ability of LFS to induce de novo LTD at Schaffer collateral-CA1 synapses in hippocampus (Reyes and Stanton, 1996). In contrast, the depotentiation of synapses where LTP had been recently induced was *not* blocked by depletion of Ca^{2+} stores, an observation directly supporting the idea that the sliding threshold for LTD is probably mediated by an increase in sensitivity to Ca^{2+} of, as yet, unidentified enzymatic targets. Mayford et al. (1995) have recently reported that transgenic enhancement of Ca^{2+}-independent, constitutively active Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) activity shifted the plasticity threshold in favor of the induction of LTD by low-frequency stimuli. Thus, CaMKII may be one enzymatic target whose sensitivity to Ca^{2+} is altered by a prior history of priming synaptic activity.

As is addressed in more detail by Wagner and Alger (1995; this issue), a key unanswered question is whether LTD represents a separate set of neuronal alterations, or if LTD, in all its many forms studied to date, is essentially "depotentiation" of potentiated synapses produced by reversal of the same changes that maintain LTP. To answer this question would require complete knowledge of the mechanisms underlying LTP, which we still lack. However, there are studies suggesting that some dephosphorylation process may be necessary for induction of LTD (Mulkey et

al., 1993, 1994). Given that protein kinase C (PKC; Lovinger et al., 1987; Malinow et al., 1989; Malenka et al., 1989) and CaMKII (Malinow et al., 1989; Malenka et al., 1989) activation are probably necessary for the induction of LTP, and that phosphorylation of both α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) and NMDA receptors by these enzymes increases their channel conductance (Tingley et al., 1993; Blackstone et al., 1994), it seems a plausible hypothesis that depotentiation LTD could be due, at least in part, to dephosphorylation of these same sites. In support of this hypothesis, Mulkey et al. (1993) have reported that inhibitors of serine/threonine protein phosphatase activity can block the induction of LFS LTD at Schaffer collateral-CA1 synapses in naive slices, and that the Ca^{2+}/calmodulin-dependent protein phosphatase calcineurin (CALC-PP, Fig. 2), by phosphorylating and inactivating inhibitor-1, may increase phosphatase activity necessary for LTD (Mulkey et al., 1994; Torii et al., 1995). These studies are at least consistent with the idea that the dephosphorylation of AMPA receptors contributes to the expression of one component of LTD.

Since cyclic AMP-dependent protein kinase (PKA) also phosphorylates glutamate receptors (Greengard et al., 1991; Wang et al., 1991), and is required for persistence of LTP (Stanton and Sarvey, 1985a,b; Stanton et al., 1989), it will be interesting to determine whether PKA plays a role in the expression of LTD. If PKA-mediated phosphorylation of protein substrates favors the expression of LTP, it may be that inhibition of PKA would shift glutamate receptor phosphorylation states in favor of LTD. However, it should be noted that ionotropic glutamate receptors are only one target for phosphorylation by all of these enzymes, and other target molecules could just as easily be responsible for the induction of LTD.

There has also been a report that inhibition of phospholipase A_2 (PLA_2) can block the induction of LTD at Schaffer collateral-CA1 synapses in the immature hippocampus (Fitzpatrick and Baudry, 1994). From their data, the authors concluded that a PLA_2 target molecule induces LTD in young animals, and LTP at later stages of development. However, given that the pharmacological agent used in these studies, bromophenacylbromide, is a completely non-selective alkylating agent capable of modifying many enzymes, their conclusions were in doubt. Recently, we reexamined this question using a more selective PLA_2 inhibitor, and found that the induction of LTP, but not LTD, was prevented by PLA_2 inhibition in both immature and adult slices (Stanton, 1995b). In addition to exonerating PLA_2 from playing a role in the induction of LTD, these experiments also indicate that there must be at least one PLA_2-sensitive target molecule that is selectively involved in the induction of LTP, but not LTD, indicating some separation in the induction mechanisms.

One recent area of excitement and controversy that has come to LTD is the study of the putative gaseous neuromodulator nitrous oxide (NO). While it has been reported that inhibitors of NO synthase, the Ca^{2+}-activated enzyme that releases NO, can block the induction of LTP (Schuman and Madison, 1991), more recent studies have indicated that the dependence of LTP on NO production may only be observed in slices at unphysiologically low temperatures (Williams et al., 1993; Cummings et al., 1994). Similarly, there has been both a recent report that NO may be involved in the induction of LTD (Izumi and Zorumski, 1993), and that production of NO is not necessary for the induction of LTD (Cummings et al., 1994). While a definitive answer still awaits, it seems likely that NO, at best, mediates only one component of long-term plasticity that may or may not be physiologically relevant, rather than an obligatory pathway for the induction of either LTP or LTD.

We have recently found that PKC, one Ca^{2+}-activated enzyme which has been implicated in the induction of LTP (Lovinger et al., 1987; Malinow et al., 1989; Malenka et al., 1989), can also regulate the sliding threshold for LTP/LTD (Stanton, 1995a). In this study, the reversible activation of PKC with phorbol ester had a number of effects on Schaffer collateral-CA1 synaptic transmission. During phorbol application, there was a marked potentiation of synaptic transmission, which slowly reversed over a 1 h drug washout. Even after the decay of the reversible phorbol-induced potentiation, two effects remained. First, application of high-frequency stimulation failed to elicit LTP, indicating a suppression of LTP similar to the activity-dependent suppression seen by Huang et al. (1992). Second, significantly larger LTD was evoked by low-frequency stimulation, indicating that PKC activation was sufficient to shift the threshold for synaptic plasticity in favor of LTD and against LTP. While these experiments suggest that one or more PKC-sensitive phosphorylation sites are able to regulate the gain and direction of synaptic plasticity, it is not yet known whether PKC activation also plays a role in the expression of LTD per se. However, our results are quite intriguing in light of the previously described work of Mayford et al. (1995), in which over-expression of CaMKII activity also shifted the threshold in favor of LTD. Since CaMKII can be a substrate for phosphorylation by PKC (Waxham and Aronowski, 1993), we propose that such a PKC-mediated phosphorylation of CaMKII could be the mechanism by which the sliding threshold is shifted in favor of LTD.

SUMMARY

LTD of synaptic transmission is a form of long-term synaptic plasticity with the potential to be as significant as LTP to both the activity-dependent development of neural circuitry and adult memory storage. In addition, interactions between LTP and LTD and the dynamic regulation of the gain of synaptic plasticity mechanisms are also very important. In particular, the computational ability of LTD to properly counterbalance LTP may be essential to maintaining synaptic strengths in the linear range, and to maximally sharpen the ability of synapses to compute and store frequency-based information about the phase relation between synapses.

Experimental data confirm the presence of an activity-dependent "sliding threshold" with the expected properties. That is, when levels of neuronal activity are high, indicating circumstances increasing the likelihood of inducing LTP, compensatory changes cause the suppression of LTP and an enhanced likelihood of LTD.

Conversely, we would predict that low levels of synaptic activity would shift the threshold in favor of greater LTP and less LTD, a hypothesis which has yet to be tested.

The sliding threshold for LTP and LTD also has implications for underlying cellular mechanisms of both forms of long-term synaptic plasticity. If the thresholds for LTP and LTD are tightly and reciprocally co-regulated, that could imply that at least one component of LTD is a true depotentiation caused by reversal of a change mediating LTP. If so, the intuitively simplest hypothesis is that phosphorylation of AMPA glutamate receptors causes LTP of synaptic e.p.s.p.s, while dephosphorylation of the same site or sites causes depotentiation LTD. Of course, this hypothesis would refer only to a postsynaptic component of both LTP and LTD. There has been a recent report that, in neonatal rat hippocampus, a form of LTD that is expressed developmentally earlier than LTP appears to have a postsynaptic induction site, but is expressed as decreased presynaptic transmitter release (Bolshakov and Siegelbaum, 1994). Whether these properties will be retained as LTD matures is unknown, as is the likelihood that, if a component of LTP is expressed presynaptically, depotentiation of that presynaptic component can also occur.

Equally unclear is the persistence of LTD relative to LTP. The few rigorous long-term anatomical studies available suggest that the latest phases of LTP may be expressed as changes in dendritic spine shapes and/or synaptic morphology. While heterosynaptic LTD has been reported to have a duration of weeks in vivo (Abraham et al., 1994), we do not know whether LTP-induced morphological changes that take many days to appear can be reversed in an activity-dependent manner. An important feature of the consolidation of memories may turn out to be the slow development of LTP that is resistant to reversal by LTD.

While we are still at an earlier stage in our understanding of the mechanisms underlying LTD compared to LTP, some things are becoming clear. LTD is induced by afferent neuronal activity that is relatively ineffective in exciting the postsynaptic cell—an "anti-hebbian" condition. This property, coupled with the hebbian properties of LTP and the dynamic nature of membrane conductances, necessarily confers upon synapses the ability to compute and store the results of a covariance function. However, the role of such a computation in processing and/or memory is unclear. In addition, LTD appears to require the activation of NMDA and metabotropic subtypes of glutamate receptors, release of Ca^{2+} from intracellular stores, and an increase in intracellular $[Ca^{2+}]$ that is lower than that necessary to induce LTP. The early evidence is consistent with some overlap of targets for modification by LTP and LTD, with some forms of LTD likely to be a reversal, or "depotentiation," of previous LTP, perhaps through dephosphorylation of AMPA receptors. The gain of both LTP and LTD appears to be regulated by the recent history of synaptic activity (minutes to hours), in a way that normalizes their strengths to maximize the dynamic range of synaptic plasticity. We propose that the mechanism by which synaptic activity shifts the LTP/LTD threshold in favor of LTD is probably through PKC phosphorylation of a particular isozyme of CaMKII, which increases its sensitivity to Ca^{2+} and yields greater CaMKII activation by subsequent synaptic inputs. While there has been exciting progress in our understanding of LTD in a short time, we still have a long way to go in integrating our knowledge of the computational rules and biochemical mechanisms of both LTP and LTD into a coherent model of functional dynamics of plastic neural circuits.

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