Long-lasting activity-dependent changes in the efficacy of synaptic transmission in the mammalian brain are considered to be of fundamental importance for the development of neural circuitry and for the storage of information. The most compelling and reliable model for such changes has been long-term potentiation (LTP) in the hippocampus, a long-lasting increase in synaptic strength normally induced by repetitive high-frequency activation of presynaptic afferents (1). With the advent of in vitro brain slice preparations and their inherent experimental advantages, an enormous effort by a cadre of researchers over the last decade has resulted in detailed (and sometimes controversial) hypotheses concerning the cellular and biochemical mechanisms responsible for LTP (2).

A nagging problem concerning the utility of LTP as either an important developmental or memory-storage mechanism has been the inability to define and characterize experimental paradigms that reliably decrease synaptic strength. Although a long-term depression (LTD) of synaptic transmission is not absolutely necessary to constrain LTP, which does exhibit a finite decay, neural networks with the ability to modify synaptic strength in both directions have enormous flexibility and power. Recently, over the last year or so, significant progress has been made in the experimental analysis of LTD in the mammalian brain. It appears that LTD, like LTP, is not a single uniform phenomenon but rather must be considered a generic term that is used to describe any long-lasting decrease in synaptic strength. Nevertheless, some common themes concerning the mechanisms of LTD in different brain regions are beginning to emerge.

Because the induction of most forms of LTD requires synaptic activation of N-methyl-D-aspartate (NMDA) receptors (one of the several subtypes of receptor activated by the excitatory neurotransmitter glutamate) during strong postsynaptic depolarization (2), LTD is considered a biological correlate of the Hebb postulate (3), which in principle predicts an increase in synaptic efficacy when presynaptic and postsynaptic activity are strongly correlated. The requirement for NMDA receptor activation also explains the important property of LTD referred to as input or synapse specificity; only those synapses activated by the LTD-inducing stimulus exhibit LTD. In contrast, early work in the hippocampus both in vivo and in vitro demonstrated that when LTP is induced in one population of synapses, a modest depression may occur at some of the inactive synapses on the same population of postsynaptic cells (4–6). In a classic paper that anticipated this finding (and that was published in this journal almost exactly 20 years ago) Stent (7) proposed that such “heterosynaptic” decreases in synaptic efficacy could be explained by an extension of the Hebb rule; synaptic strength will decrease at inputs that are quiescent or weakly active when the postsynaptic cell is very active. While theoreticians over the ensuing two decades convincingly demonstrated the importance of algorithms that could decrease synaptic strength (8–10), experimental work on LTD lagged far behind, especially when compared to the enormous effort aimed at understanding the mechanisms of LTP.

Thus, several years ago, considerable excitement was generated by the report that LTD could be generated in the CA1 region of hippocampal slices when synaptic inputs were stimulated either out-of-phase with short bursts of stimuli given to an independent conditioning input or during direct hyperpolarization of the postsynaptic cell (11). This LTD was of particular interest because it was “homo- and homosynaptic,” occurring only at those synapses activated by the stimulation, and because its induction obeyed the converse of the Hebb rule (i.e., synapses were weakened when their activity did not correlate with significant postsynaptic activity). Unfortunately, disappointment soon followed as many laboratories had difficulty replicating this phenomenon (12). However, optimism and enthusiasm are on the rise recently as it appears that there are indeed forms of LTD that are amenable to rigorous experimental attack (not only in the hippocampus but also in the cerebellum and cerebral cortex). A common theme that emerges from the results to date is that, like LTP, changes in postsynaptic Ca²⁺ levels are required for the generation of LTD, although the specific characteristics of this Ca²⁺ signal may differ.

In the CA1 region of the hippocampus, prolonged, low-frequency (1 Hz) afferent stimulation produces a saturable and stable homosynaptic (i.e., synapse-specific) LTD (13, 14). Surprisingly, the induction of this form of LTD is quite similar to LTP in that it requires activation of NMDA receptors (13, 14) and is blocked by strong hyperpolarization or buffering postsynaptic Ca²⁺ (14). Homosynaptic LTD has much in common with previous reports of “depotentiation” following LTD (15, 16); in fact, recent evidence suggests that homosynaptic LTD and LTP are reversal modifications of some common expression mechanism (17). However, a significant difference between homosynaptic LTD and LTP may be their developmental profile, since LTD appears to be more robust in slices prepared from young animals (14, 17).

The mechanisms of heterosynaptic LTD have also been examined recently in the CA1 region of hippocampal slices. This form of LTD is often quite small in magnitude (18) or requires unusual induction conditions (i.e., complete blockade of synaptic transmission during induction) (19). Nonetheless, changes in postsynaptic Ca²⁺ again appear to be required, although in this case Ca²⁺ is supplied via activation of voltage-dependent Ca²⁺ channels (18, 19).

In the cerebellum, an absolute requirement for the LTD of the parallel fiber (PF)-Purkinje cell (PC) synapse induced by simultaneous climbing-fiber (CF) activation is a rise in postsynaptic Ca²⁺. The evidence includes the following observations: (i) CF activation can be replaced by direct depolarization of PCs (20, 21), (ii) both manipulations result in large increases in dendritic Ca²⁺ level (21), and (iii) LTD is blocked by loading PCs with Ca²⁺ chelators (21, 22) or by removing external Ca²⁺ (20). Activation of a metabotropic glutamate receptor (20, 23) possibly coupled to activation of protein kinase C (24) also appears to be necessary for cerebellar LTD. Questions that remain about this form of LTD include whether activation of the synaptic non-NMDA receptor is necessary for
LTD induction (20) and whether release of nitric oxide plays a critical role (25).

Understanding the mechanisms of synaptic plasticity in the cerebral cortex is perhaps the most exciting and challenging goal for synaptic physiologists—exciting because the cortex is the site primarily responsible for long-term information storage and challenging because, unlike the hippocampus and cerebellum, cortical circuitry does not readily lend itself to a detailed stimulation of defined inputs and recording of defined monosynaptic responses. Despite these technical obstacles, the mechanisms of LTD in cortex are beginning to emerge. In slice preparations of different regions of cortex, LTD can be elicited by tetanic stimulation in the presence of NMDA receptor antagonists (26-28). Since, like other forms of LTD, corticall LTD is blocked by buffering postsynaptic Ca\(^{2+}\) with buffers, a role for voltage-dependent Ca\(^{2+}\) channels or Ca\(^{2+}\) release from intracellular stores has been proposed (29, 30). The strong dependence of the induction of LTD in neocortex (26) is the only evidence at this point that is consistent with a role for voltage-dependent Ca\(^{2+}\) channels. However, a recent paper (31) presents several lines of evidence consistent with the suggestion (32) that activation of a subtype of metabotropic glutamate receptor coupled to inositol phosphate turnover and the consequent release of Ca\(^{2+}\) from 1,4,5-inositol trisphosphate-sensitive stores is sufficient to elicit LTD in cortex. In this set of experiments, LTD was generated by repetitively applying a tetanus during blockade of NMDA and non-NMDA receptors with antagonists (an unusual protocol that had previously been used successfully in hippocampal slices; ref. 19). Loading cells with guanosine 5′-(β-thio)diphosphate, heparin, or Ca\(^{2+}\) chelators all blocked LTD, and the phenomenon could be mimicked by bath application of quisqualate, a metabotropic glutamate receptor agonist.

It is well established that a rise in postsynaptic Ca\(^{2+}\) is necessary for LTP induction (33, 34). How can a rise in postsynaptic Ca\(^{2+}\) also be responsible for LTD? If the possibility that an increase in postsynaptic Ca\(^{2+}\) is necessary but not sufficient to change synaptic efficacy and that additional factors are required. Some studies in the hippocampus may be considered consistent with this hypothesis (35, 36), although in neocortex simply adjusting the postsynaptic membrane potential during a tetanus has been reported to determine whether LTD or LTP ensues (26). Another suggestion has been that the magnitude of Ca\(^{2+}\) increase determines the direction of synaptic change with relatively small changes causing LTD (19, 26, 30). Taking advantage of the different affinities of biochemical probes for Ca\(^{2+}\)/calmodulin, a model (37) has demonstrated how the quantitative level of postsynaptic Ca\(^{2+}\) may control synaptic efficacy by adjusting the relative activities of Ca\(^{2+}\)/calmodulin-dependent protein kinase II and phosphatase I. One potential problem with these simple hypotheses is that, at least in hippocampal CA1 pyramidal cells, sustained synaptic stimulation appears to be necessary to generate homosynaptic LTD (13, 14), and manipulations that dampen the magnitude of a brief Ca\(^{2+}\) signal do not result in LTD but instead elicit a transient synaptic enhancement known as short-term potentiation (STP) (38, 39). Thus, temporal properties of the Ca\(^{2+}\) signal may also be quite important for controlling synaptic strength.

A second critical question is whether the source of the Ca\(^{2+}\) signal (NMDA receptors, voltage-dependent Ca\(^{2+}\) channels, and intracellular stores) matters. During blockade of NMDA receptors, an increase in synaptic strength can be generated by repetitive activation of voltage-dependent Ca\(^{2+}\) channels (36, 40, 41) or, in some cases, by activation of metabotropic glutamate receptors (42, 43). When voltage-dependent Ca\(^{2+}\) channels are repetitively activated, the large bolus of dendritic Ca\(^{2+}\) may overcome endogenous buffering mechanisms and may activate biochemical processes in dendritic spines normally activated by Ca\(^{2+}\) influx via NMDA receptor channels (44). Similarly, perhaps the Ca\(^{2+}\) signal involved in heterosynaptic LTD in the hippocampus mimics that occurring during the induction of homosynaptic LTD. Why activation of metabotropic glutamate receptors causes LTD at some synapses and is required for LTD at others remains a mystery, although an obvious possibility is the known heterogeneity in subtypes of this class of glutamate receptor (45).

Testing whether the induction of one form of LTD occludes the subsequent generation of a distinct form should go a long way in clarifying whether the forms of LTD described to date share common cellular mechanisms and thus whether the source of the requisite postsynaptic Ca\(^{2+}\) change matters. Whatever the outcome of future experiments, those interested in synaptic plasticity can rejoice because LTD is no longer an only child; a sibling is now on the scene and will demand all of the attention that any toddler deserves.