LTP and LTD: Dynamic and Interactive Processes of Synaptic Plasticity

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Long-lasting, activity-dependent changes in the efficacy of synaptic transmission are considered to be of fundamental importance for the storage of information and for the development of neural circuitry. The leading experimental model for such a change has been long-term potentiation (LTP), a long-lasting increase in synaptic strength. Intensive experimental analysis of LTP in the hippocampus has resulted in a detailed description of the initial steps responsible for its generation. Recently, a form of long-term depression (LTD) in the hippocampus has been described and examined. It shares several mechanistic features with LTP and appears to be able to reverse LTP. The intracellular second messenger systems that are required to generate and maintain LTP and LTD have been difficult to identify definitively. Leading candidates include diffusible intercellular messengers as well as protein kinases and protein phosphatases, the activities of which may converge at the level of specific phosphoproteins. In addition to delineating the cellular mechanisms underlying LTP and LTD, investigators also are beginning to clarify the roles they play in real learning and memory.
The Neuroscientist 1:35–42, 1995

KEY WORDS *Synaptic plasticity, Long-term potentiation, Long-term depression, Hippocampus, Memory*

One of the most remarkable features of the mammalian central nervous system is its ability to store large amounts of information for periods approaching a lifetime. How does the brain accomplish this feat? As long ago as the turn of the century, the Nobel prize-winning neuroanatomist Ramon y Cajal proposed that memories may be due to long-lasting, activity-dependent changes in the strength of synaptic transmission in critical neural circuits (1), a hypothesis that later was refined by several other prominent neuroscientists (2, 3). The essential concept was that because external (and internal) events are represented in the brain by spatiotemporal patterns of neuronal activity, when some new piece of information is learned and remembered, this same neural activity must result in modifications of synaptic strength in the neural circuits that were activated. The intuitive appeal of this idea, it is hoped, will become apparent if one considers the everyday process of remembering a telephone number.

As the theoretical importance of long-lasting activity-dependent changes in synaptic strength became apparent, neuroscientists initiated a search for such a phenomenon in the mammalian brain. It was not until 1973, however, that a remarkable success was reported. Bliss and his colleagues (4, 5) found that brief trains of high-frequency stimulation applied to excitatory afferents to the hippocampus caused an increase in the strength of synaptic transmission that could last for days or even weeks in intact animals. Since its discovery, this long-term potentiation (LTP) of excitatory synaptic transmission in the hippocampus has become the primary experimental model for examining the synaptic mechanisms of learning and memory and, as such, has been the subject of intense experimental scrutiny over the last decade.

The excitement surrounding the study of LTP arises from several sources. First, compelling evidence derived primarily from lesion studies in higher primates including man indicates that the hippocampus is a critical component of a neural system in the medial temporal lobe, which is required for the initial storage of certain forms of long-term memory (6). Second, LTP exhibits several properties that confirm theoretical predictions originally made by Hebb (2), making it an attractive cellular mechanism for information storage or memory. Like memory, LTP can be generated rapidly and is prolonged and strengthened with repetition. It exhibits input-specificity, which indicates that LTP only occurs at synapses that are stimulated by a given pattern of afferent activity but not at adjacent, unstimulated synapses on the same postsynaptic cell (Fig. 1). By limiting the number of synapses on a given cell that are modified by afferent activity, the storage capacity of a

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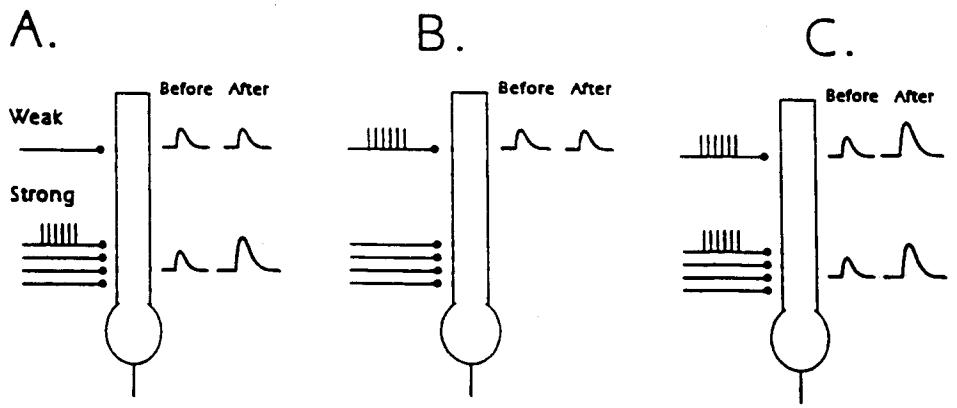

Fig. 1. Diagram showing the basic properties of LTP. A single pyramidal cell is shown receiving a weak and a strong synaptic input. *A*, tetanic stimulation of the strong input alone causes LTP in the strong input (compare the excitatory postsynaptic potentials before and after the tetanus) but has no effect on the weak input. *B*, tetanic stimulation of the weak input alone has no effect on synaptic strength. *C*, tetanic stimulation of both the strong and weak inputs together now causes LTP in both inputs. Modified with permission from (7).

neural circuit is dramatically increased. Perhaps most importantly, LTP is associative. This indicates that activity in an input that is strong enough to elicit LTP can help generate LTP in synapses on the same cell activated by a "weak input" (incapable of eliciting LTP by itself) if the activity in the two inputs occurs within a finite temporal window (Fig. 1). The associative property of LTP is reminiscent of classical conditioning and is often considered a cellular analog of associative learning. A third source of excitement about LTP is that it can be elicited in reduced in vitro preparations of hippocampus. This makes it amenable to rigorous experimental manipulations, the results of which can then be applied to physiological and behavioral experiments performed in vivo. Finally, the cellular, biochemical, and molecular processes responsible for LTP may also contribute to the neuronal damage that occurs as a consequence of a variety of CNS insults, such as strokes or seizures, or during neurodegenerative diseases. Thus, in addition to providing clues to the cellular basis of learning and memory, the study of LTP may contribute to our understanding of pathophysiological processes in the CNS and thereby to the development of rational therapies.

Although there are several different forms of LTP that are found in several different brain regions, including many areas of cerebral cortex, most experimental work has focused on the LTP observed in hippocampal CA1 pyramidal cells. It is this form of LTP that will be the focus of the remainder of this review.

The Induction of LTP: A Critical Role for NMDA Receptors and Calcium

LTP normally is generated by activating a number of synapses simultaneously at a relatively high frequency (20–200 Hz). A large body of experimental evidence (reviewed in 8 and 9) indicates that this tetanic stimulation provides the essential requirements for generating LTP: strong depolarization of the postsynaptic cell at a time when the excitatory neurotransmitter glutamate has been released from presynaptic terminals and acts upon postsynaptic glutamate receptors. How can these requirements explain all of the properties of LTP that were described above? During normal low-frequency synaptic transmission, glutamate binds to two different types of postsynaptic receptors that are colocalized on a dendritic spine (Fig. 2). The AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate) receptor channel, which is permeable primarily to Na^+, provides the majority of current responsible for generating synaptic responses at the resting membrane potential (−60 to −80 mV). In contrast, the NMDA (N-methyl-D-aspartate) receptor contributes only a small fraction to the postsynaptic response, because extracellular Mg^{2+} sits in and blocks its ion channel. When the postsynaptic membrane is depolarized during the induction of LTP, however, Mg^{2+} is expelled from the NMDA receptor channel, allowing Ca^{2+} as well as Na^+ to enter the cell. With repeated activation of NMDA receptors during adequate postsynaptic depolarization, Ca^{2+} builds up in the dendritic spine to a high level and activates the signaling mechanisms responsible for LTP. Thus, the NMDA receptor can be thought of as a molecular coincidence detector that permits Ca^{2+} influx only when afferent activity occurs in conjunction with depolarization of the target dendrite. This model explains why LTP only occurs at stimulated synapses; NMDA receptors must be activated by synaptically released glutamate so that they can permit Ca^{2+} influx. It also explains the associative induction of LTP; the depolarization provided by activity in the strong input (Fig. 1) helps to depolarize the adjacent synapses activated by the weak input. Consistent with this idea, LTP can be generated simply by "pairing" low-frequency afferent activity with postsynaptic depolarization provided by the recording electrode (11).

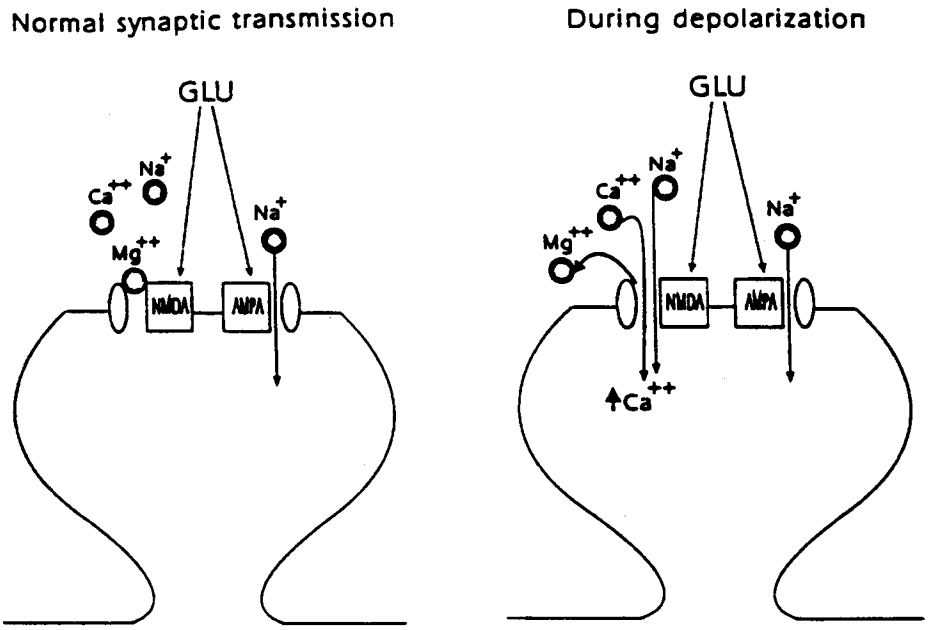

Fig. 2. Model for the induction of LTP. During normal synaptic transmission, glutamate (GLU), which is released from the presynaptic terminal, acts on both NMDA and AMPA receptors. Na^+ flows through the AMPA receptor channel but not through the NMDA receptor channel because of the Mg^{++} block of this channel. Depolarization of the postsynaptic cell relieves the Mg^{++} block of the NMDA receptor channel, allowing Na^+ and Ca^{++} to flow into the cell. The resultant rise in Ca^{++} in the dendritic spine is a necessary trigger for subsequent events leading to LTP. Reprinted with permission from (10).

The evidence demonstrating a mandatory role for NMDA receptors and Ca^{2+} in the induction of LTP is compelling. First, NMDA receptor antagonists completely block the generation of LTP while having minimal effect on basal synaptic transmission (12). Second, synaptic activation of NMDA receptors has been shown directly to result in an accumulation of Ca^{2+} within dendritic spines (13, 14). Third, buffering increases in Ca^{2+} by loading CA1 cells with Ca^{2+} chelators prevents LTP (15, 16). Fourth, increasing Ca^{2+} directly in CA1 cells can enhance synaptic transmission and, thus, at least mimic LTP (16).

Although NMDA receptors are thought to be the primary source for the rise in $[Ca^{2+}]_i$ required to generate LTP, other sources of Ca^{2+}, including voltage-dependent Ca^{2+} channels and release from intracellular stores, may also contribute or even be required under certain circumstances. Recent evidence also suggests that the triggering event for LTP may not simply be a switch-like mechanism that is activated by some threshold level of $[Ca^{2+}]_i$. Instead, it appears that the duration or "stability" of LTP is not fixed but, in part, depends on the degree of activation of NMDA receptors and perhaps the magnitude of increase in $[Ca^{2+}]_i$ within the spine (17, 18). A final important question concerning the role of Ca^{2+} in LTP induction is whether a large rise in $[Ca^{2+}]_i$ alone is sufficient to generate stable LTP. Experiments testing this hypothesis suggest that afferent synaptic activity may provide some additional essential ingredient (19), a prime candidate being activation of metabotropic glutamate receptors by synaptically released glutamate (20). Metabotropic glutamate receptors are members of the large family of G protein-coupled receptors and, as such, can cause stimulation of a number of second messenger signaling pathways.

Signal Transduction Mechanisms in LTP

Given that a rise in postsynaptic $[Ca^{2+}]_i$ is a critical trigger for generating LTP, an important question is what are the biochemical mechanisms activated by Ca^{2+} that are, at least in part, responsible for LTP. This question has generated much research that has considered many candidate molecules, yet relatively little is known about the specific molecules involved in LTP and the exact roles they fulfill. Much of the work on the signal transduction path that converts the initial trigger signal for LTP into long-lasting modifications of synaptic proteins has focused on the role of protein kinases. This is not surprising because phosphorylation is an ubiquitous biochemical mechanism that plays an important role in many cell functions, and protein kinases are found in very high concentrations in the mammalian brain. The protein kinases that have received the most attention are Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), protein kinase C (PKC), and, more recently, the tyrosine kinase, Fyn. When injected into CA1 pyramidal cells, inhibitors of these enzymes block LTP (21–23) and two of them (CaMKII and PKC) have been shown to be activated by tetanic stimulation that elicits LTP (24–26). An intriguing hypothesis is that the long-lasting nature of LTP is due to the maintenance of increased protein

kinase activity (reviewed in 27). This might occur as a consequence of the autophosphorylation of CaMKII, which makes it independent of Ca^{2+}-calmodulin or the proteolytic cleavage of the regulatory domain of PKC. Biochemical experiments have provided correlative evidence in support of this idea (24–26), but the results of physiological experiments directly testing this hypothesis have been less clear.

It was hoped that gene-targeting approaches, which permit the generation of mutant mice lacking a specific protein, might clarify the exact role of some of these enzymes in LTP. However, "knock-outs" of the most ubiquitous isoforms of CaMKII and PKC (α-CaMKII and PKCγ, respectively) or of Fyn have not yielded easily interpretable LTP phenotypes. In all of these mutants, it appeared that although LTP was more difficult to elicit, it was not absent, despite the absence of gene product (28, 29). Given the possibility in such mice of compensatory and redundant mechanisms in the LTP signaling cascade, without much further work, these results will remain difficult to interpret. Thus, there is reasonably good evidence that several protein kinases are involved in LTP, but their exact roles and targets remain to be defined.

The Multiple Phases of LTP and Gene Expression

Behavioral studies indicate that memory can be divided into different stages, most simply, short-term and long-term memory. Similarly, LTP exhibits several phases that can be distinguished on the basis of their time course and the requirement for new protein synthesis. The first phase, which occurs immediately after the tetanic stimulation used to induce LTP, is transient, lasting anywhere from 10 to 60 minutes and is termed *short-term potentiation* (STP). STP can be induced in isolation of LTP by using stimulation protocols that activate NMDA receptors but are subthreshold for generating LTP (17) or by activating voltage-dependent Ca^{2+} channels (19). Its mechanistic relationship to LTP remains unclear (18), although recent work suggests that like LTP, it is dependent on CaMKII (30). Following STP is an "early," more stable component of LTP (often termed LTP1) that lasts on the order of 1 to 3 hours and that does not appear to require new protein synthesis. In hippocampal slices, LTP1 is followed by a late stage of LTP that lasts up to 10 hours and that is dependent on protein synthesis. In the intact animal, this late stage of LTP is much longer-lasting and can be divided into two additional protein synthesis-dependent components, LTP2 and LTP3, that last for several days and several weeks, respectively.

Whereas enzymatic modification of preexisting synaptic proteins may be sufficient to change synaptic efficacy for modest periods of time, in the context of the continuous turnover of proteins, it seems necessary to invoke additional mechanisms to account for the maintenance of LTP for days or weeks. Recent work indicates that these later components of LTP may, in fact, involve altered gene expression due to the activation of immediate early genes (IEGs). IEGs are normally expressed at low levels in quiescent cells but can be rapidly and transiently activated by a variety of extracellular signals, including synaptic activity (31). Many IEGs encode transcription factors and, thus, they provide a mechanism by which synaptic activity can directly influence gene expression (31). Tetanic stimulation in vivo is associated with increased mRNA and protein levels of several IEGs (32), but the generation and persistence of LTP seems most closely associated with the activation of the transcription factor *zif268* (33, 34). The signal transduction pathway by which NMDA receptor activation activates *zif268* and perhaps other transcription factors is unknown. One prominent component of this pathway may by PKA (the cAMP-dependent protein kinase), which appears to play an important role in the late stage of LTP in hippocampal slices (35).

The Expression of LTP: A Role for Retrograde Messengers?

Although it is firmly established that the initial triggering events for LTP occur in the postsynaptic cell, it has been difficult to establish unequivocally whether the final increase in synaptic strength is due to pre- and/or postsynaptic modifications. The most recent work on this issue has applied the methods and assumptions of quantal analysis. The basis for this approach derives from classic experiments at the neuromuscular junction where neurotransmitter is contained in multimolecular packets of constant size known as quanta. After nerve stimulation, these are released in a probabilistic fashion such that the variability in response size can be analyzed statistically to estimate the probability of neurotransmitter release and the size of the postsynaptic response to a single quantum. During LTP, an increase in quantal amplitude has been observed, a finding that is consistent with a postsynaptic change. However, a decrease in the percentage of times a presynaptic stimulus fails to elicit a postsynaptic response also occurs with LTP as does a decrease in the variability of responses. According to classic assumptions, both of these changes are consistent with an increase in the probability of transmitter release during LTP. These apparently contradictory results have been reconciled by proposing that both pre- and postsynaptic changes occur during LTP, the relative contribution of each depending on the initial probability of transmitter release at the stimulated synapses.

It is important to note that the interpretation of the quantal analysis results is limited by the unproven assumption that hippocampal synapses behave just like the neuromuscular junction. Moreover, LTP could be accompanied by novel and unexpected synaptic changes that would result in an improper interpretation

of results. For example, if synapses existed that contained only NMDA receptors and no or nonfunctional AMPA receptors (so-called "silent" synapses, because under normal conditions, release of glutamate from the presynaptic terminal would not elicit a postsynaptic response), LTP might involve the insertion or uncovering of functional AMPA receptors at these synapses. Such a mechanism could explain many of the quantal changes that classically would be interpreted as due to presynaptic, not postsynaptic, modifications (36, 37).

Assuming that presynaptic changes accompany LTP, these must be caused by the production of a retrograde messenger that is released from the postsynaptic cell and diffuses backward across the synaptic cleft so as to affect the presynaptic terminal (reviewed in 38). The first candidate retrograde messenger to be considered was arachidonic acid, a product of eicosanoid metabolism that caused a synaptic enhancement when accompanied by presynaptic activity (39). More recently, however, attention has focused on the potential role of nitric oxide (NO), which is produced after the NMDA receptor-dependent activation of the Ca^{2+}/calmodulin-dependent enzyme, nitric oxide synthase. Support for a role for NO in LTP comes from the demonstration that inhibitors of NO synthase may block LTP, and application of NO may enhance neurotransmitter release in an activity-dependent but NMDA receptor-independent fashion (reviewed in 40). However, the production of NO is not absolutely required to generate LTP (reviewed in 41), raising the possibility that NO plays some regulatory, rather than mandatory, role in LTP. It is also conceivable that when production of NO is blocked, parallel or redundant processes take over so that LTP can still be generated. Additional retrograde messengers may include carbon monoxide or platelet-activating factor (see 41). If a diffusible factor is released during the generation of LTP, an intriguing possibility is that it can diffuse away from the synapses at which it was produced and affect synaptic efficacy at adjacent synapses on neighboring cells (42).

Long-Term Depression: What Goes Up Should Come Down

If memories are created by modifying spatiotemporal patterns of synaptic activity, it would seem that the flexibility and storage capacity of neural circuits would be significantly increased if synaptic efficacy could be decreased as well as increased. Theoretical work with neural networks has, in fact, demonstrated the many advantages of incorporating algorithms that allow for bidirectional control of the strength of connections. It also has long been recognized that the activity-dependent phase of neural circuit development, during which some synapses are stabilized and others are pruned, would benefit from the presence of mechanisms that allow for depression, as well as potentiation, of synaptic efficacy.

Despite the knowledge that activity-dependent decreases in synaptic strength may be just as important for nervous system functions as activity-dependent increases, until recently, work on long-term depression (LTD) has lagged far behind that on LTP. However, this situation is beginning to change, and it is now apparent that like LTP, LTD exists in a number of different brain regions (43). It is generally classified as homosynaptic or heterosynaptic, depending on whether the decrease in synaptic strength occurs at the stimulated synapses only (homosynaptic) or also at inactive synapses that are adjacent to the activated portion of the dendritic tree (heterosynaptic). The remainder of this review will focus on a recently described form of LTD in the hippocampus, which appears closely related to LTP.

In CA1 pyramidal cells, LTD is normally generated by prolonged (3–15 minutes) low frequency (1–2 Hz) afferent stimulation. Surprisingly, it shares many features with LTP (44–46). It is homosynaptic, indicating that only the input receiving the repetitive stimulation undergoes LTD, whereas other inputs onto the same cell are unaffected. It is also saturable such that repeated periods of low-frequency stimulation cannot depress synaptic strength to below about 50% of control values. The relative magnitude of LTD shows a significant age dependence; slices from 2-week-old animals exhibit LTD that is double that observed in slices from 5-week-old animals. Perhaps the most interesting feature of LTD is its ability to reverse LTP. Synapses that have been potentiated can be depressed and vice versa. Indeed, it is possible to repeatedly increase and decrease synaptic strength above and below its initial value simply by changing the pattern of afferent activity. The reversal of LTP by low-frequency stimulation is often called "depotentiation." Mechanistically, depotentiation appears to be identical to LTD (see below), but unlike LTD, it is robust in adult as well as young animals (47). The reasons for this are unclear, with one possibility being that there is a limited dynamic range over which synaptic strength can be altered and that in tissue prepared from older animals, synapses are more likely to be in their depressed state (41).

Mechanisms of LTD

Many of the initial steps responsible for the induction of LTD are known, and they, surprisingly, are remarkably similar to those responsible for generating LTP. Like LTP, LTD is blocked by NMDA receptor antagonists and by buffering changes in postsynaptic $[Ca^{2+}]_i$. These results force the conclusion that induction of homosynaptic LTD requires entry of Ca^{2+} through the NMDA receptor channel. This can occur because, at the resting membrane potential, the voltage-dependent block of the NMDA receptor channel by Mg^{2+} (Fig. 2) is not 100% effective and, thus, each stimulus will cause

a very small, but not nonexistent, current through the NMDA receptor channel, some of which is carried by Ca^{2+}. Under some circumstances, Ca^{2+} entry through voltage-dependent Ca^{2+} channels may also generate LTD, although normally this is a heterosynaptic form (reviewed in 48).

How can an NMDA receptor-mediated rise in $[Ca^{2+}]_i$ be involved in both LTP and LTD? One possibility mentioned previously is that an increase in $[Ca^{2+}]_i$ may be necessary, but not sufficient, to cause changes in synaptic efficacy and as yet unidentified factors may be required. Alternatively, a more popular current hypothesis is that specific properties of the Ca^{2+} signal, including its magnitude and perhaps its temporal structure, may alone completely determine the direction of synaptic change caused by synaptic activity. If Ca^{2+} is the triggering signal for LTD, it must be capable of activating biochemical processes that reverse LTP. Because LTP is due, at least in part, to activation of postsynaptic protein kinases, a reasonable hypothesis is that LTD is due to preferential activation of protein phosphatases, some of which are known to be found in isolated synaptic junctions (49).

This idea was first presented by Lisman (50) who proposed a simple but specific model that accounted for bidirectional control of synaptic strength by Ca^{2+} (Fig. 3). In principle, it proposed that a balance between the activity of CaMKII and protein phosphatase I (PP1) influences synaptic strength by controlling the phosphorylation state of some unidentified phosphoproteins. Small rises in $[Ca^{2+}]_i$ favored activation of PP1, whereas larger rises were necessary for increasing CaMKII activity. Because, unlike CaMKII, PP1 is not directly influenced by $[Ca^{2+}]_i$, a well-established Ca^{2+}-dependent protein phosphatase cascade (49) was invoked to translate the Ca^{2+} signal into an increase in PP1 activity. This cascade (Fig. 3) begins with activation of the Ca^{2+}/calmodulin-dependent phosphatase calcineurin (also known as protein phosphatase 2B; PP2B). Calcineurin then dephosphorylates inhibitor 1, a phosphoprotein, which in its phosphorylated state is a potent inhibitor of PP1. Thus, activation of calcineurin causes an increase in PP1 activity by a mechanism of disinhibition.

Several experimental results are consistent with this model. Pharmacological inhibitors of PP1 or calcineurin, when loaded directly into CA1 cells, prevent the generation of LTD (51, 52). Furthermore, the phosphorylated form of inhibitor 1, but not the unphosphorylated form, blocked LTD (52). An attractive feature of this model is that calcineurin has a higher affinity for Ca^{2+}/calmodulin than does CaMKII and therefore would be preferentially activated by small rises in $[Ca^{2+}]_i$.

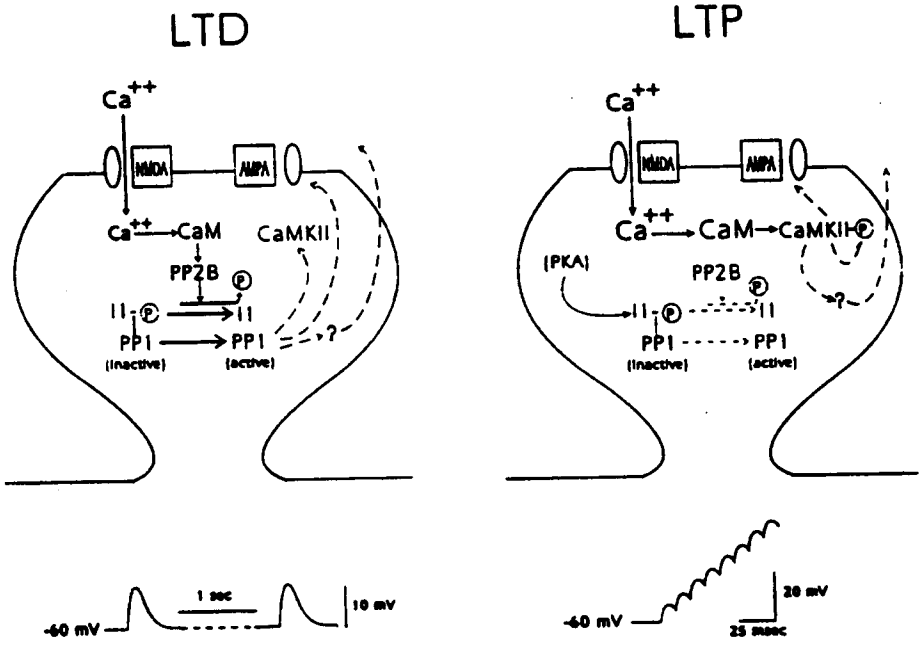

Fig. 3. Model for the signaling cascades responsible for LTD and LTP. During prolonged 1-Hz stimulation (shown as traces below the LTD dendritic spine) Ca^{++} enters the dendritic spine via the NMDA receptor channel and causes a small rise in Ca^{++}. Ca^{++} binds to calmodulin (CaM), which preferentially activates calcineurin (PP2B). Calcineurin then dephosphorylates inhibitor 1 (I1), which therefore no longer inhibits protein phosphatase 1 (PP1). Active PP1 may act upon any number of substrates including CaMKII, AMPA receptor subunits, or some unknown process that influences the production of retrograde messengers. During high-frequency stimulation (shown as traces below the LTP dendritic spine), a large amount of Ca^{++} enters the dendritic spine via the NMDA receptor channel. Ca^{++} again binds to CaM and preferentially activates CaMKII. Active CaMKII may act on the same substrates as those modified during LTD. The cAMP-dependent protein kinase (PKA) also may be activated by high Ca^{++} and phosphorylate I1. Reprinted with permission from (10).

The activation of protein phosphatases by synaptic activity also may play an important role in modulating the threshold for the induction of LTP. It has been demonstrated that several different patterns of afferent activity, including some that produce LTD in young rats, can make it more difficult subsequently to elicit LTP (47, 53, 54). This inhibitory effect of prior synaptic activity on LTP induction decays over the course of an hour (53) and is blocked by phosphatase inhibitors (54), suggesting that it is due to the transient activation of protein phosphatases.

Although the dissection of the biochemical mechanisms responsible for LTP and LTD is still relatively crude, the current evidence suggests that the control of synaptic efficacy at these synapses may be under the regulation of a complicated network of interacting and mutually regulatory signaling cascades, the functions of which are, in part, to control the phosphorylation state of critical substrate phosphoproteins. Which cascade dominates at any given instance may depend on the spatial and temporal dynamics of changes in $[Ca^{2+}]_i$, which are profoundly influenced by synaptic activity. Many of the signaling molecules implicated in LTP and LTD themselves may be regulated by phosphorylation, lending additional complexity to the dynamic interactions between the processes responsible for LTP and LTD.

The idea that synaptic strength is determined by the phosphorylation state of certain synaptic phosphoproteins may prove overly simplistic. Nevertheless, the discovery of a form of LTD that reverses LTP should greatly facilitate future efforts at understanding the cellular and biochemical mechanisms of hippocampal synaptic plasticity.

Learning and Memory: A Role for Synaptic Plasticity?

Although LTP is the leading candidate for a synaptic mechanism responsible for the encoding of memory, is it actually used during real learning to store information? This is a difficult question to address experimentally, and a conclusive answer cannot be given at this time, but several lines of evidence are consistent with an important role for LTP (and perhaps LTD) in certain forms of learning and memory. First, in rodents in which the hippocampus is particularly important for spatial memories, infusion of an NMDA receptor antagonist blocks LTP induction and spatial learning at the same concentrations, while having no effect on a visual discrimination task that does not require hippocampal function (55). Second, the targeted gene knockouts of various protein kinases that impaired LTP also impaired spatial learning (28, 56), although the degree of deficit in learning did not necessarily directly correlate with the degree of impairment in LTP. Third, as a rat explores a novel environment and presumably learns about it, increases in synaptic efficacy in the hippocampus occur that are not due to the motor activity itself (57). Final correlative evidence is provided by the recent elegant study in which simultaneous ensemble recordings of 75–150 hippocampal neurons were made while a rat explored a familiar or novel environment (58). When the animal was learning about the novel space, the activity of inhibitory interneurons was suppressed, a condition that would facilitate synaptic modifications. Furthermore, neurons that fired together during this behavior also exhibited increased correlated activity during sleep, an effect that is readily explained by the occurrence of modifications in synaptic efficacy during waking (59).

To definitively prove that activity-dependent changes in synaptic strength are responsible for the encoding of memories is a daunting task. Nevertheless, as presaged by several of this century's preeminent neuroscientists (1–3), the mechanisms underlying synaptic plasticity should continue to provide the strongest clues to the experimental analysis of the physical substrate of memory well into the next century.

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