**Synaptic Plasticity in the Hippocampus: LTP and LTD**

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Perhaps the most fundamental and remarkable feature of the mammalian central nervous system is its ability to process and store large amounts of information. For many decades it has been postulated that the brain uses long-lasting modifications of synaptic strength in critical neural circuits to accomplish this feat. One such activity-dependent modification is long-term potentiation (LTP) in the hippocampus, a sustained increase in synaptic strength that is elicited by brief high frequency stimulation of excitatory afferents. Recent excitement about the phenomenon of LTP has arisen from three major sources. First, compelling evidence from lesion studies in higher primates, including humans, shows that the hippocampus is a critical component of a neural system that is required for the initial storage of certain forms of long-term memory (Squire and Zola-Morgan, 1991). Second, several properties of LTP make it an attractive cellular mechanism for information storage or memory (Bliss and Collingridge, 1993). Like memories, LTP can be generated rapidly and is strengthened with repetition. It exhibits input specificity; that is, LTP occurs only at synapses stimulated by afferent activity but not at adjacent synapses on the same postsynaptic cell. Input specificity presumably dramatically increases the storage capacity within a neural circuit. Most importantly, LTP is associative; temporally pairing activity in a “weak” input (incapable of generating LTP by itself) with activation of a strong input (capable of eliciting LTP in the hippocampus) can result in a sustained increase in synaptic strength that is due to the maintenance of increased protein synthesis (Squire and Zola-Morgan, 1991). This makes it amenable to rigorous experimental manipulations.

There are several different forms of LTP, but the majority of experimental work has focused on the LTP observed in hippocampal CA1 pyramidal cells. This minireview will provide an update on the cellular mechanisms of LTP and distinguish those mechanisms that are firmly established from those that remain contentious. The evidence connecting LTP to real learning and memory also will be reviewed briefly.

The **Induction of LTP: NMDA Receptors and Ca**

It is well accepted that the induction of LTP requires activation of postsynaptic N-methyl-d-aspartic acid (NMDA) receptors (a subtype of glutamate receptor) during postsynaptic depolarization, which is normally generated by high frequency afferent activity. This results in a rise in Ca\(^{2+}\) concentration ([Ca\(^{2+}\)]\(_\text{I}\)), a necessary trigger for LTP. Figure 1 shows that during normal low frequency synaptic transmission, the excitatory neurotransmitter glutamate is released from a presynaptic terminal and binds to postsynaptic NMDA and \(\alpha\)-amino-3-hydroxy-5-methyl-4-isoxazolopropionate (AMPA) receptors that are colocalized on a dendritic spine. The AMPA 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 receptor does not contribute to the postsynaptic response because extracellular Mg\(^{2+}\) sits in and blocks its ion channel. When the postsynaptic membrane is depolarized during the generation of LTP, Mg\(^{2+}\) is expelled from the cell. With repeated activation, sufficient Ca\(^{2+}\) enters the dendritic spine to activate the signaling mechanisms that result in LTP. Thus, the NMDA receptor functions as a molecular coincidence detector that allows Ca\(^{2+}\) influx only when afferent activity occurs in conjunction with depolarization in the target dendrite.

Although there is much evidence supporting the preceding model (Bliss and Collingridge, 1993), recent work suggests that the triggering event for LTP may not be a simple switch-like mechanism that is activated by some threshold rise in [Ca\(^{2+}\)]. For example, the duration or stability of LTP is not fixed but appears to be dependent on the degree of activation of NMDA receptors and perhaps the magnitude of increase in [Ca\(^{2+}\)] within the spine (Malenka and Nicoll, 1993). Moreover, a large rise in [Ca\(^{2+}\)] alone may be insufficient to generate stable LTP; afferent activity may provide some additional essential ingredient (Kullman et al., 1993). One possibility is that glutamate, in addition to activating NMDA receptors, must also activate metabotropic glutamate receptors (Bashir et al., 1993), which typically are coupled to phosphoinositide turnover.

**Protein Kinases and Signal Transduction Mechanisms in LTP**

The majority of work on the signal transduction path that converts the initial trigger signal for LTP into long-lasting modifications of proteins has focused on the role of protein kinases, in particular Ca\(^{2+}\)/calmodulin-dependent protein kinase II (CaMKII), protein kinase C (PKC), and the tyrosine kinase Fyn. Inhibitors of these enzymes can block LTP (see Bliss and Collingridge, 1993), and two of them (CaMKII and PKC) have been shown to be activated in an NMDA receptor-dependent manner by tetanic stimulation that elicits LTP (Fukunaga et al., 1993; Klann et al., 1993; Sacktor et al., 1993). An attractive hypothesis has been that LTP is due to the maintenance of increased protein kinase activity (see Schwartz, 1993). This might occur as a consequence of the autophosphorylation of CaMKII or the proteolysis or phosphorylation of PKC. Correlative evidence in support of this idea comes from recent biochemical experiments in which protein kinase activity stayed elevated for 30–90 min following LTP induction (Fukunaga et al., 1993; Klann et al., 1993; Sacktor et al., 1993). It was anticipated that gene-targeting approaches might clarify the exact role of some of these enzymes, but "knockouts" of a CaMKII, PKCy, or Fyn have not yielded an easily
Normal synaptic transmission
During normal synaptic transmission, glutamate (GLU) acts on both NMDA and AMPA receptors. Na⁺ flows through the AMPA receptor channel but not through the NMDA receptor channel because of the Mg²⁺ block of this channel. Depolarization of the postsynaptic cell relieves the Mg²⁺ block of the NMDA receptor channel, allowing Na⁺ and Ca²⁺ to flow through this channel. The resultant rise in Ca²⁺ in the dendritic spine is a necessary trigger for subsequent events leading to LTP.

The Interpretation of LTP Phenotypes
In all of these mutants, it appeared that LTP was more difficult to elicit but was not absent (Grant and Silva, 1994; Abeliovich et al., 1993). 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, at this point, the evidence suggests that several protein kinases are involved in LTP, but their exact roles and targets are obscure.

The Expression of LTP and Retrograde Messengers
While there is little dispute that the events responsible for the initial generation of LTP occur in the postsynaptic cell, no question has been more difficult to answer than perhaps the simplest one: is the final increase in synaptic strength due to pre- or postsynaptic modifications? Over the last decade, the pendulum has swung back and forth several times, and the final answer has yet to be completely settled. Early reports of an increase in the overflow of radiolabeled or endogenous glutamate during LTP favored a presynaptic change in neurotransmitter release. However, a postsynaptic change in glutamate receptor sensitivity was suggested by an increase in response size to exogenous application of glutamate agonists (see Bliss and Collingridge, 1993).

More recently, attempts were made to apply the general methods and assumptions of quanta1 analysis to LTP. The basis for this approach comes from classic work at the neuromuscular junction where neurotransmitter is contained in multimolecular packets of constant size known as quanta. Following nerve stimulation, these are released in a probabilistic fashion, and the resultant 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, there appears to be a decrease in the percentage of times a presynaptic stimulus fails to elicit a postsynaptic response and 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. However, an increase in quantal amplitude also has been observed during LTP, a finding that is consistent with a postsynaptic change. These contradictory results have been reconciled by the proposal that both pre- and postsynaptic changes occur during LTP, the relative contribution of each depending on the initial probability of release at the stimulated synapses.

The interpretation of these quanta1 analysis results is limited by the assumption that central nervous synapses behave just like the neuromuscular junction. To eliminate the influence of any incorrect assumptions, two groups (Manabe et al., 1992; Malgaroli and Tsien, 1992) examined miniature synaptic responses that are due to the spontaneous release of quanta. Because only a few percent of the sampled synapses on a pyramidal cell can be stimulated electrically, both groups used application of glutamate or NMDA to mimic the generation of LTP. In hippocampal slices, an increase in the amplitude of miniature events was observed with a minimal change in their frequency, findings consistent with an increased postsynaptic sensitivity to glutamate (Manabe et al., 1992). In contrast, in cultured hippocampal cells, the main effect of activation of postsynaptic NMDA receptors was to increase the frequency of miniature events (Malgaroli and Tsien, 1992). This result is most readily explained by an enhancement in presynaptic transmitter release.

It is relatively easy to envision a mechanism by which activation of postsynaptic processes during LTP induction results in a change in postsynaptic receptor sensitivity (e.g., glutamate receptor phosphorylation). However, postsynaptic changes during LTP require production of a retrograde messenger that is released by the postsynaptic cell and diffuses backward across the synaptic cleft so as to affect the presynaptic terminal. The first retrograde messenger to receive attention was arachidonic acid, a product of eicosanoid metabolism that caused a synaptic enhancement when accompanied by presynaptic activity (Williams et al., 1989). However, since NMDA receptor activation presumably is only necessary to generate the retrograde messenger, any exogenously applied retrograde messenger should enhance synaptic strength during blockade of NMDA receptors, and this may not occur with arachidonic acid (O'Dell et al., 1991). Great excite-
ment has been raised by the possibility that NMDA receptor activation causes activation of the Ca\textsuperscript{2+}/CaM-sensitive form of nitric oxide synthase. This results in the release of nitric oxide, which might enhance neurotransmitter release in an activity-dependent and NMDA receptor-independent fashion (Zhuo et al., 1993; see Schuman and Madison, 1994a). However, the production of nitric oxide may not be absolutely required to generate LTP (Williams et al., 1993), raising the possibility that it plays some regulatory role, perhaps adjusting the threshold for LTP induction. Alternatively, when nitric oxide production is blocked, parallel or redundant processes may take over so that LTP can still be generated. These additional retrograde messengers may include carbon monoxide (Stevens and Wang, 1993; Zhuo et al., 1993) or platelet-activating factor (Kato et al., 1994).

**Distributed Potentiation**

A basic property of LTP is thought to be synapse specificity; LTP occurs only at those synapses in which Ca\textsuperscript{2+} is raised by activating NMDA receptors during adequate postsynaptic depolarization. However, if LTP involves release of a diffusible messenger, this messenger might interact with adjacent synapses on the same cell or even on the synapse of a neighboring cell. Evidence for the latter phenomenon has been presented in an elegant study that required simultaneous intracellular recording from two adjacent cells (Schuman and Madison, 1994b). Inducing LTP in an input to one cell caused LTP of the synapses of that same input onto a neighboring cell. This occurred only if the somata of the two cells were within approximately 150 \textmu m. Anatomical staining of these cells revealed that their dendritic arbors overlapped extensively, suggesting that a diffusible messenger that is produced by one cell would have to travel only a short distance to affect synapses on the neighboring cell. Surprisingly, LTP in the neighboring cell was prevented by a Ca\textsuperscript{2+} chelator and strong hyperpolarization. This result does not indicate whether the messenger acts pre- or postsynaptically, but it does indicate that some Ca\textsuperscript{2+}- or voltage-dependent process in the postsynaptic cell is required to observe the effects of the messenger.

**Long-Term Depression: What Goes Up Usually Comes Down**

If memories are stored in spatial patterns of synaptic strengths, it would be advantageous to be able to decrease, as well as increase, synaptic strength so as to increase the flexibility and storage capacity of a neural circuit. Many forms of long-term depression (LTD) have been described (Linden, 1994), but one that is closely related to hippocampal LTD has been examined in detail only during the last 2 years (Dudek and Bear, 1992; Mulkey and Malenka, 1992). It is normally generated by prolonged low frequency (1 Hz) stimulation and appears to be due to a reversal of the processes responsible for LTP. Surprisingly, this form of LTD shares several features with LTP. It is input specific and requires activation of NMDA receptors as well as some rise in postsynaptic [Ca\textsuperscript{2+}]. How can an NMDA receptor-mediated rise in [Ca\textsuperscript{2+}] be involved in both LTP and LTD? A simple hypothesis is that properties of the Ca\textsuperscript{2+} signal (e.g., magnitude, temporal pattern) control the direction of change in synaptic strength by activating different subsets of signaling cascades. One simple model that accounts for bidirectional control of synaptic strength by Ca\textsuperscript{2+} is presented in Figure 2 (modified from Lisman, 1989). It proposes that a balance between the activity of CaMKII and protein phosphatase 1 (PP1) influences synaptic strength by controlling the phosphophorylation state of some unidentified phosphoprotein(s). Small rises in [Ca\textsuperscript{2+}] favor activation of PP1 while larger rises are necessary for increasing CaMKII activity. Because, unlike CaMKII, PP1 is not directly influenced by [Ca\textsuperscript{2+}], a well-established Ca\textsuperscript{2+}-dependent protein phosphatase cascade that involves activation of calmodulin and dephosphorylation of inhibitor 1 was invoked to translate the Ca\textsuperscript{2+} signal into an increase in PP1 activity (Lisman, 1989). Recent work using inhibitors of PP1, CaM, and calmodulin has confirmed several features of this model (Mulkey et al., 1993, 1994).
Although the idea that synaptic strength is determined by the phosphorylation state of certain phosphoproteins will likely prove too simplistic, the discovery of a form of LTD that reverses LTP should facilitate future efforts at understanding the mechanisms of synaptic plasticity in the hippocampus. LTD also puts constraints on mechanistic hypotheses of hippocampal synaptic plasticity. For example, assuming that LTP requires a retrograde messenger that modifies presynaptic proteins, then LTD must require a different retrograde messenger or be due to a decrease in some constitutively produced retrograde messenger.

**Synaptic Plasticity: Its Role in Learning and Memory**

A fundamental question concerning LTP has been whether it actually is used during learning to store memories. Although a conclusive answer cannot be given, work using rodents (in which the hippocampus is critically important for spatial memory) suggests that an LTP-like process may indeed be important for certain forms of learning and memory. First, an NMDA receptor antagonist blocks LTP induction and spatial learning at the same concentrations (Davis et al., 1992) while having no effect on a visual discrimination task that does not require hippocampal function. Second, the targeted gene knockouts of various genes that impair LTP generation also impaired spatial learning (Grant and Silva, 1994; Abellovich et al., 1993). However, the degree of deficit in learning did not correlate with the degree of impairment in LTP. It is worth noting that NMDA receptor antagonists block both LTD and LTP and that LTD was normal in the PKCδ mutant mice that exhibited the mildest behavioral deficit. Thus, a plausible hypothesis is that both forms of synaptic plasticity (LTP and LTD) contribute to efficient learning.

If changes in synaptic efficacy are important for the encoding of spatial information, then it should be possible directly to record such changes as an animal explores a novel environment. This was observed several years ago, although the significance of this behaviorally induced increase in synaptic strength was questioned because of the demonstration that an increase in brain temperature due to motor activity, in and of itself, could account for the observed changes. This issue has been addressed experimentally by subtracting the changes in synaptic strength due to temperature (Moser et al., 1994). When this is done, hippocampal synaptic potentiation does occur as an animal explores a familiar or novel environment (Wilson and McNaughton, 1993). When the animal was learning about the novel space, the activity of inhibitory interneurons were suppressed, a condition that would facilitate synaptic modifications.

To prove that long-lasting changes in synaptic efficacy are responsible for the encoding of memory remains a daunting task. Nevertheless, the excitement about hippocampal synaptic plasticity should remain unabated since the mechanisms underlying LTP and LTD provide the strongest clues for the experimental analysis of the physical substrate of memory. It seems probable that synaptic efficacy, like other fundamentally important cellular phenomena, will turn out to be controlled by a complicated network of interacting signaling cascades that are regulated at multiple levels. This complexity presents a formidable experimental challenge, but perhaps by the time the next minireview in Cell about this topic is due (see Kennedy, 1989), the expanding multidisciplinary attack on hippocampal function will provide a more definitive answer to the question of how the brain encodes memories.

**References**


