Long-Term Synaptic Potentiation

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Long-term synaptic potentiation (LTP) is a leading candidate for a synaptic mechanism of rapid learning in mammals. LTP is a persistent increase in synaptic efficacy that can be quickly induced. The biophysical process that controls one type of LTP is formally similar to a synaptic memory mechanism postulated decades ago by the psychologist Donald Hebb. A key aspect of the modification process involves the *N*-methyl-D-aspartate (NMDA) receptor–ionophore complex. This ionophore allows calcium influx only if the endogenous ligand glutamate binds to the NMDA receptor and if the voltage across the associated channel is also sufficiently depolarized to relieve a magnesium block. According to one popular hypothesis, the resulting increase in the intracellular calcium concentration activates protein kinases that enhance the postsynaptic conductance. Further biophysical and molecular understanding of the modification process should facilitate detailed explorations of the mnemonic functions of LTP.

DISCOVERING THE PHYSICAL BASIS OF LEARNING IN HUmans and other mammals is among the greatest remaining challenges facing the neurosciences. One of the oldest and most popular ideas holds that learning involves use-dependent modifications in the strengths of preexisting synaptic connections among neurons [for review, see (*1*)]. Theoretical studies have shown that networks of processing elements with modifiable interconnections can indeed display powerful associative learning and self-organizational capabilities (*2*). Neurobiological studies of learning in higher invertebrates have convincingly demonstrated that certain forms of Pavlovian conditioning do in fact result from activity-dependent changes in synaptic efficacy (*3*). These studies have motivated the search for analogous synaptic mechanisms for information storage in mammals. The phenomenon of LTP is a leading candidate for this function.

The LTP hypothesis for learning has captured the attention of neuroscientists working at several different levels of organization—molecular, cellular, systems, and behavioral. This review (i) explains what LTP is and why there has been such an explosion of interest in this phenomenon; (ii) summarizes several hypotheses regarding the biophysical and molecular mechanisms underlying LTP; (iii) identifies some of the technical developments that are driving the current growth in our understanding of this extraordinary form of synaptic plasticity; and (iv) poses a challenge to researchers in this field. This challenge is to provide a convincing linkage between LTP and learning and to elucidate how endogenously generated LTP mediates its mnemonic functions.

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Properties of LTP

LTP was first described in the rabbit hippocampal formation by Bliss and colleagues (*4*). The essence of LTP is a rapid and persistent synaptic enhancement (*4–6*). By rapid we mean that the modification can be induced by brief (tens of milliseconds) stimulation of an afferent input (usually at 100 to 400 Hz). By persistent we mean that it outlasts previously discovered forms of synaptic enhancement such as facilitation, augmentation, and posttetanic potentiation (PTP) [see table 1 of (*7*)]. Of the latter, PTP is the most persistent, typically lasting a few (1 to 10) minutes after a brief stimulation. LTP is not unique to the hippocampal formation (*6, 8*), but it has only been reported at excitatory synapses (*5, 7*).

In neurophysiological studies that utilize intracellular recording techniques, the synaptic enhancement is measured as the increase in the amplitude of the excitatory postsynaptic potential (EPSP) or the excitatory postsynaptic current (EPSC) produced by a single-pulse stimulation of an afferent input. Almost all intracellular recordings of LTP have been performed on the brain slice preparation [reviewed in (*7*)]. In studies that employ extracellular recording techniques, enhancement is measured as an increase in the amplitude or the slope of some component of the field potential produced by stimulating the afferent input. Extracellular (field potential) recordings suggest that LTP can remain stable in vivo for weeks or possibly months (*9*). The maximum duration of LTP in vitro is uncertain. Usually the posttetanic synaptic enhancement is only monitored for 15 to 60 min in brain slices. In such experiments LTP is commonly defined as any use-dependent synaptic enhancement that clearly outlasts PTP.

Varieties of LTP. There are several different types of LTP. Racine and co-workers have examined the time course of the enhancement in vivo and suggested that different forms of LTP can be classified based on decay time constants (*9*). In studies of brain slices a discrimination is sometimes made between "decremental" LTP (which decays over the course of tens of minutes) and "nondecremental" LTP (which shows little or no detectable decay over this time period) (*10*). Comparative studies have suggested that it might be reasonable to separate associative types of LTP from other types (*6–8, 10–14*). Another way to categorize varieties of LTP is based on whether the induction of the modification is dependent on the activation of particular types of receptors (*7, 10, 11*). One must therefore recognize that several different mechanisms may be included within the class of synaptic modifications that are called LTP (*11*). The following discussion is mainly concerned with an NMDA receptor–dependent form of associative LTP.

Associative LTP. High-frequency (tetanic) stimulation is not always sufficient to induce LTP. In some synaptic systems, the intensity of the electrical shocks delivered in the tetanic stimulation is important (*4, 5, 15*). Low-intensity stimulation fails to induce LTP in these systems. There are several possible interpretations of this intensity effect (*5, 7, 10, 11, 15*). One interpretation is that LTP induction depends on the strength of the postsynaptic response during the tetanic stimulation. The postsynaptic response amplitude

depends on the number of stimulated afferents, which in turn depends on the stimulus intensity. According to this interpretation, tetanic stimulation of a small number of afferent inputs fails to induce LTP because these inputs collectively produce a weak (**W**) postsynaptic response. Tetanic stimulation of a larger number of afferent inputs succeeds in inducing LTP because these inputs produce a strong (**S**) postsynaptic response. This intensity effect, which has been demonstrated at two of the three most commonly studied synaptic systems of the hippocampus, is relevant to the phenomenon of associative LTP (*11–13, 16*).

Associative LTP refers to a particular type of interaction between separately and independently stimulated **W** and **S** synaptic inputs to a neuron (*12, 13, 16*). The nature of the interaction that defines associative LTP is taken from the perspective of the **W** input. It is a synaptic enhancement that can be induced in the **W** input if both the **W** and the **S** input are stimulated together at about the same time, but not if each is stimulated separately at very different times or if only one of them is stimulated (*1, 11–13, 16*). Activity in the **S** input enables enhancement to occur in just those **W** inputs that are eligible for change by virtue of being active at about the same time (*11, 16*).

The synaptic activity–enhancement relations that govern associative LTP are pertinent to its possible role as a synaptic substrate for learning. These relations include the following (*11–13, 16*): (i) The induction of the modification is rapid; (ii) the enhancement of synaptic strength is persistent; (iii) the modification in one synaptic input can be conditionally controlled by temporal contiguity with activity in another input to the same region; and (iv) the associative enhancement appears to be specific to just those synapses that are active at the proper time. These are also features of the synaptic mechanisms that underlie simple forms of associative memory in the marine mollusk *Aplysia* (*3*).

Hebbian form of LTP. The spatiotemporal features of associative LTP (*11, 16*) can be accounted for by the type of learning mechanism postulated several decades ago by the psychologist Donald Hebb (*17*). The following passage has come to be known as Hebb's postulate for learning (*17*):

> When an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased.

The evolution of the contemporary concept of a Hebbian synaptic modification is reviewed elsewhere (*1*). The core idea is a use-dependent synaptic enhancement based on an interaction between concurrent pre- and postsynaptic activity (*1, 18*). A Hebbian mechanism explains associative LTP as follows: The EPSC generated by the **S** input allows the required co-occurrence between presynaptic activity in the **W** input and some critical level of postsynaptic depolarization in the target cell. Because the essential interaction between pre- and postsynaptic activity only occurs if the **W** and **S** inputs are stimulated at about the same time, this mechanism confers a high degree of spatiotemporal specificity.

The Hebbian interpretation was tested directly in the hippocampus (*19*) by substituting for the usual **S** input a combination of current- and voltage-clamp procedures that either prevented or forced simultaneous pre- and postsynaptic spiking activity (Fig. 1). A synaptic input was repetitively stimulated under either of two extreme conditions—while applying a voltage clamp to the soma of the postsynaptic neuron to prevent postsynaptic action potentials and somatic depolarization (Fig. 1A, left traces) or while applying a simultaneous depolarizing current step to force action potential firing in the postsynaptic neuron (Fig. 1A, right traces). The microelectrode-injected current was similar in magnitude and duration to the current normally produced by the **S** input during a tetanic stimulation.

Neither postsynaptic activity alone nor synaptic stimulation conducted while applying a voltage clamp to the postsynaptic cell soma produced LTP (Fig. 1C). However, LTP was induced when presynaptic stimulation was paired with simultaneous postsynaptic depolarization (Fig. 1C). The interactive mechanism also had the required spatiotemporal specificity to account for what was known about associative LTP (*11–13, 16*). The Hebbian nature of this type of hippocampal LTP is one of the best documented and least controversial findings in this field. In 1986, four independent groups reported similar findings (*19, 20*).

Mechanisms of LTP

The problem of understanding LTP mechanisms can be divided into three parts (*5–8, 11*). The initial sequence of events that triggers or sets into motion the modification process is termed "induction." The set of mechanisms that constitute the proximal cause of the synaptic enhancement is called "expression." The factors that govern the duration of the enhancement are referred to as "maintenance." A complete understanding of LTP requires investigation of each of these aspects and the way in which they interact (Fig. 2).

Induction of LTP. The experiments of Kelso *et al.* (*19*) demonstrated that some consequence of postsynaptic depolarization enables LTP induction at just those synapses that are eligible to change by virtue of being concurrently active. By injecting the postsynaptic cells with a local anesthetic, they further showed that the postsynap-

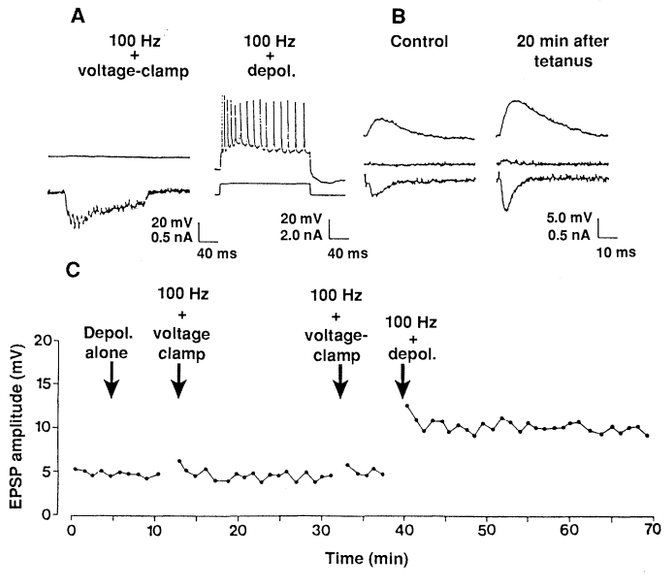

Fig. 1. Direct demonstration of the interactive mechanism. All recordings are of Schaffer collateral synaptic responses in hippocampal neurons of region CA1. (**A**) (Left) Voltage-clamp record of inward synaptic currents (lower trace) and membrane potential (upper trace) during the synaptic stimulation train. (Right) Current-clamp recording of postsynaptic action potentials (upper trace) produced by an outward current step (lower trace) that is paired with the synaptic stimulation train. (**B**) Current-clamp (top traces) and voltage-clamp (bottom traces) records before and 20 min after pairing synaptic stimulation with the outward current step. Middle trace is the membrane potential during voltage clamp. (**C**) EPSP amplitudes as a function of the time of occurrence (arrows) of three manipulations: an outward current step alone (Depol. alone) or synaptic stimulation trains delivered while applying either a voltage clamp (100 Hz + voltage clamp) or an outward current step (100 Hz + depol.). Each point is the average of five consecutive EPSP amplitudes. Modified from (*19*).

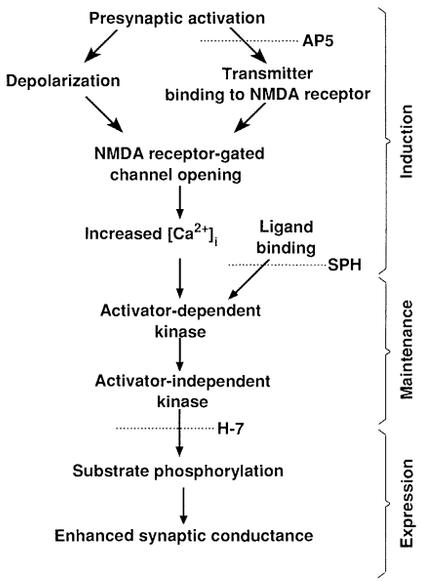

Fig. 2. Summary of some key events suspected to participate in various aspects of LTP. The conjunction of transmitter binding and postsynaptic depolarization causes the opening of Ca^{2+}-permeable channels and a resulting increase in the intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$). The neurotransmitter binding step can be blocked by AP5. Activation of protein kinases is mediated by elevated $[Ca^{2+}]_i$ plus binding of particular ligands to the enzyme. The kinase activation step can be blocked by SPH. The kinase can become activator-independent, at which point SPH does not block the catalytic activity. Either form of the kinase can phosphorylate a substrate that ultimately causes synaptic enhancement. Substrate phosphorylation can be reversibly blocked by H-7.

tic contribution to this interactive mechanism does not require the elicitation of Na^+-dependent action potentials. The induction step appears instead to be controlled by the NMDA subtype of receptor for glutamate (*21, 22*), which is thought to be a neurotransmitter in these synapses. The key observation was that antagonists for the NMDA receptor, such as DL-2-amino-5-phosphonopentanoate (AP5), block LTP induction but neither prevent the expression of LTP that has already been induced nor impair ordinary synaptic transmission (*21, 22*). The voltage- and neurotransmitter-dependent gating of Ca^{2+} influx through the NMDA receptor–associated channels (*23, 24*) suggests an attractive explanation for the Hebbian interactive mechanism (Fig. 2).

The NMDA receptor–ionophore complex must receive two signals simultaneously to become highly permeable to Ca^{2+}: glutamate must be bound to the NMDA receptor and the membrane must be sufficiently depolarized to relieve a Mg^{2+} block of the channel that occurs at voltages close to the normal resting potential (*23, 24*). The Mg^{2+} block is relieved when the membrane is depolarized to levels achieved by tetanic stimulation of the **S** input. When the Mg^{2+} block is removed, glutamate binding to the NMDA receptor causes the associated channel to open to a 50-pS conductance state that is permeable to Ca^{2+} (*23, 24*).

It is easy to see how the properties of the NMDA receptor–ionophore complex can account for aspects of associative LTP if we assume that an increase in the Ca^{2+} concentration in some postsynaptic compartment of the cell is necessary for LTP induction (*25*). Tetanic stimulation of a **W** input causes presynaptic glutamate release but fails to depolarize the membrane enough to relieve the Mg^{2+} block. Stimulating a **W** input therefore fails to induce LTP unless the stimulation is accompanied by strong postsynaptic depolarization produced by either a microelectrode or by an **S** input (*16, 19, 20*). To explain the input specificity requires further consideration of the spatial distribution of the postsynaptic Ca^{2+} signal. If we assume that the critically involved NMDA receptors are on the heads of the dendritic spines, then the peak transient increase in the Ca^{2+} concentration will be restricted to the immediate region of the stimulated synapses (*7, 11, 26*).

The working hypothesis shared by many laboratories is that Ca^{2+} serves as a second messenger or cofactor to trigger enzyme translocation or activation (*25, 27, 28*). A popular extension of this idea is that a Ca^{2+}-dependent protein kinase plays an essential role in the mechanisms of LTP (*27–29*). Activation of certain protein kinases, including Ca^{2+}-calmodulin–dependent protein kinase (CamKII) and Ca^{2+}-phospholipid–dependent protein kinase (PKC), requires both a critical Ca^{2+} concentration and binding of a ligand (calmodulin or lipids) to the enzyme (*27, 28, 30*) (Fig. 2). These kinases can act as switches (*30*) in that they can be converted to an activator-independent form, requiring neither Ca^{2+} nor ligand for catalytic activity (*31, 32*). For this reason the duration of the catalytic activity can greatly exceed the duration of the activators.

Maintenance of LTP. Some recent pharmacological discoveries are furnishing intriguing clues into enzymatic events that may control the maintenance of LTP (*27, 28*). One notion is that the maintenance of LTP depends on conversion of a protein kinase to an activator-independent form (see Fig. 2). Supporting evidence comes from studies of the effects on LTP of sphingosine (SPH), which blocks PKC and CamKII activation by preventing ligand binding (*28, 31*). When present prior to tetanic stimulation, SPH prevents LTP (*28*). However, SPH does not suppress LTP when added after tetanic stimulation (*28*). One interpretation is that LTP is maintained by an activator-independent protein kinase (*28, 32*).

Expression of LTP. If LTP is in fact maintained by the continued activity of a protein kinase (*28, 29*) [as opposed to the presence of a long-lived phosphorylated substrate (*27*)], then blocking the catalytic activity of the kinase should suppress the expression of LTP. The catalytic activity of two enzymes that have been suggested to participate in LTP—CamKII and PKC—can be reversibly blocked by H-7 (*32*). When added after a tetanic stimulation, H-7 reversibly suppresses the expression of LTP (*28*).

The expression of LTP ultimately involves an increase in the measured postsynaptic conductance (*7, 11, 33*). There is no evidence that LTP is accompanied by generalized changes in the excitability or the passive membrane properties of the postsynaptic neurons (*12, 33*). Elsewhere we consider at length three plausible explanations for the increase in the measured synaptic conductance (*7, 11*): an increase in transmitter release (*5*); an increase in the sensitivity of the postsynaptic membrane to released transmitter (*29*); and a decrease in the series resistance of dendritic spines (*34*).

There is compelling evidence that some forms of LTP involve a presynaptic modification that increases transmitter release (*5, 6, 8*), but in most synapses there is no basis for ruling out other possibilities. Hebbian synapses in particular would seem to be logical candidates for a postsynaptic modification. However it is theoretically possible that the induction of the modification occurs on the postsynaptic side of the cleft and that the expression of the enhancement involves a presynaptic change (*5, 7, 11, 35*).

Significance of LTP

LTP has attracted so much interest for three reasons. First, it is the type of modification that connectionist theories of learning have long envisioned. Second, recent technical advances make it possible to understand in great detail the molecular and biophysical mechanisms responsible for this type of use-dependent modification in synapses from the mammalian brain. Third, the knowledge generated by these technical advances will enable explorations of the role of particular synaptic modifications in the development and organization of behavior in mammals.

Psychology, computation, and physiology. The idea of a Hebb-like physiological mechanism for learning can be traced back at least to the end of the 19th century (*1*). The psychologist William James (*36*), writing in 1890 about the physiological basis of associative

memory, proposed a "law of neural habit" that can be seen as an antecedent to Hebb's (*17*) postulate for learning. Hebb's theory has become refined and quantified by the rapidly expanding field of computational neuroscience (*1, 37, 38*). Theoretical studies have shown that useful and potentially powerful forms of learning and self-organization can emerge in networks of elements that are interconnected by various formal representations of a Hebbian modification (*38*). This theoretical work thus amplified the significance of the subsequent neurophysiological discovery (*19, 20*) of a Hebbian synaptic mechanism in the hippocampus.

The growth of in vitro technology. The spectacular technical progress that has been made in the past decade has created great optimism that we shall soon be able to understand in considerable depth the mechanisms that control the induction, maintenance, and expression of LTP. A large part of this new technology involves in vitro methods that enable detailed study of identifiable classes of synapses of the adult mammalian brain. Three such methods are being combined to study LTP: the acute brain slice preparation (*14, 39*), the single microelectrode current- and voltage-clamp technique (*7, 10, 11, 14, 19, 33*), and improved visualization procedures for imaging cellular and subcellular neuronal structures in living brain slices (*7, 11, 40*). This combination of methods enables experiments on synapses of the adult mammalian brain that previously could only be done in the vertebrate peripheral nervous system, certain invertebrate ganglia, or in cell cultures. Further developments in optical techniques combined with a new generation of molecular probes promise to open up additional experimental opportunities (*41*).

Linking LTP to learning. The significance of LTP ultimately rests on its functional role. The challenge to researchers in this field is to demonstrate that LTP is endogenously generated and to elucidate the nature of its involvement in the development and organization of behavior. The goal of exploring linkages to learning is becoming more attainable as we discover the molecular and biophysical mechanisms that control the induction, maintenance, and expression of LTP. Such knowledge provides experimental tools that can be used to explore the possibility that endogenously generated LTP participates in some aspect of learning or memory.

If LTP does in fact serve a mnemonic function, then pharmacological agents that specifically block the induction step might be expected to interfere with the acquisition of new associations but not the retention of old associations. One study that was designed to explore this possibility (*42*) demonstrated that intraventricular administration of AP5 prevents learning a new spatial memory task without affecting retention of previously learned behaviors. Conversely, drugs that specifically impair the maintenance or expression of LTP might be expected to affect retention but not initial acquisition. The effects of agents such as SPH and H-7 on acquisition and retention have not yet been explored.

Pharmacological manipulations are not the only avenue available for exploring linkages to learning. Another approach has been to determine whether LTP induction affects subsequent learning. Two studies have shown that learning is in fact influenced by electrical stimulation procedures that induce LTP in the hippocampus (*43*).

We must admit that the evidence linking LTP to learning is not yet convincing (*44*). However the explosion of new experimental technologies available for studying mammalian synapses will surely generate knowledge about LTP mechanisms that can be used to probe the functional role of this intriguing form of neuroplasticity (*45*).

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The Neural Basis for Learning of Simple Motor Skills

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The vestibulo-ocular reflex (VOR) is a simple movement that has been used to investigate the neural basis for motor learning in monkeys. The function of the VOR is to stabilize retinal images by generating smooth eye movements that are equal and opposite to each head movement. Learning occurs whenever image motion occurs persistently during head turns; as a result image stability is gradually restored. A hypothesis is proposed in which the output from the cerebellar cortex of the flocculus guides learning; the locus of learning is in the brain stem, in VOR pathways that are under inhibitory control from the flocculus. Other, parallel VOR pathways do not receive inputs from the flocculus and are not subject to learning. Similarities among the VOR and other motor systems suggest some organizing principles that may apply in many forms of motor learning.

COMPLEX MOTOR PATTERNS SUCH AS THE PLAYING OF A Beethoven piano sonata or the fielding and throwing of a baseball are not executed correctly on the first attempt. Rather, initial efforts are corrected, refined, and finally (sometimes) perfected by a process that involves making errors, detecting them through sensory inputs and correcting the errors on subsequent repetitions of the movement. The process that improves motor performance through practice is called motor learning.

Much has been discovered about the neural and cellular basis for learning in invertebrate species (*1*), but little is known about how learning occurs in intact mammals. We think that motor learning provides a unique opportunity to understand learning in mammals, because motor activity generates a tangible output that can be measured in the laboratory. To identify the neural networks that subserve specific movements and to determine how and where each network is modified in association with learning, we have investigated the neural networks that mediate a simple example of motor learning in monkeys.

Eye movements as a model system for learning. Eye movements have a number of advantages that make them an excellent model system for investigating both normal brain function and learning in adult primates. Just a few muscles are used to move the eyes, and many of the neural networks that provide inputs for those muscles have been identified. Indeed, the past 20 years has seen a massive effort in the study of the neural basis for eye movement (*2*). The result is a strong conceptual and technical foundation for conducting experiments on learning in the oculomotor system of awake, behaving monkeys.

The primate oculomotor repertoire consists of several kinds of eye

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