REVIEW

Yan-You Huang, Peter V.
Nguyen, Ted Abel, and
Eric R. Kandel¹

Howard Hughes Medical Institute and
Center for Neurobiology and Behavior
College of Physicians and Surgeons of
Columbia University
New York, New York 10032

Long-lasting Forms of Synaptic Potentiation in the Mammalian Hippocampus

Introduction

Memory storage in the mammalian brain is commonly divided into at least two distinct temporal phases: short-term memory, lasting minutes to hours, and long-term memory, which can persist for days, weeks, or even years (for review, see Polster et al. 1991). Whereas short-term memory requires only covalent modifications of pre existing proteins, long-term memory requires the synthesis of new mRNA and protein (Davis and Squire 1984; Castellucci et al. 1989; Tully et al. 1994).

The idea that memory storage in the brain results from activity-dependent changes in synaptic strength was elaborated by Hebb (1949), who proposed that synapses linking two cells could be strengthened if both cells were active simultaneously. The first such Hebbian synapses to be found in the mammalian brain were the connections made by entorhinal perforant path fibers onto dentate granule cells in the hippocampus (Bliss and Lomo 1973). Brief, high-frequency stimulation of this excitatory pathway elicited a long-lasting enhancement of synaptic transmission. This effect, now known as long-term potentiation (LTP), can last for 8–10 hr in hippocampal slices, and for several days and even weeks in intact animals. LTP has now been shown in all three major monosynaptic excitatory pathways within the hippocampus (the perforant pathway, mossy fiber pathway, and Schaffer collateral pathway) (Bliss and Collingridge 1993).

Hippocampal LTP has a number of properties that make it an attractive model for memory storage. These include associativity, synapse specificity, cooperativity, and persistence (see Bliss and Collingridge 1993 for a more complete description). In this review, we will focus on the long-term maintenance (late phase) of LTP and its underlying mechanisms. We will try to illustrate how pharmacological and molecular biological approaches, some with genetically modified animals, have elucidated some of the mechanisms that contribute to long-term changes in synaptic strength. Most of the experiments that we will discuss use the hippocampal slice preparation, and they focus on synaptic changes occurring over hours. Thus, these changes pertain primarily to the initial phase of the cellular changes that contribute to long-term memory storage. Other, still longer term changes in synaptic strength that may occur over days or weeks can be studied in the intact animal, but these will not be discussed here.

¹Corresponding author.

The Early and Late Phases of LTP Have Distinct Induction Requirements and Temporal Characteristics

Activity-dependent synaptic potentiation can be divided into a number of mechanistically distinct temporal phases. These include post-tetanic potentiation (PTP), short-term potentiation (STP), the early phase of LTP (E-LTP), and the late phase of LTP (L-LTP). PTP lasts for, at most, a few minutes following high-frequency stimulation. STP decays within 15–20 min, and is distinguished from LTP by the requirement of LTP for protein kinase activity (Bliss and Collingridge 1993). E-LTP lasts for about 1–3 hr and is distinguished from L-LTP, which lasts for up to 8–10 hrs in slices, by the requirement of L-LTP for protein kinase A activity, protein synthesis, and RNA synthesis (Frey et al. 1993; Huang and Kandel 1994; Nguyen et al. 1994).

The existence of these several forms of synaptic potentiation raises the question: What are the induction requirements for each? STP requires only a single weak train of stimulation (50 Hz, 0.5 sec; Malenka and Nicoll 1993). E-LTP, lasting 1–3 hr, is generally induced in the mossy fiber and Schaffer collateral pathways with one train (1 sec) of 100-Hz stimulation (Huang and Kandel 1994; Huang et al. 1994). However, in the medial perforant pathway, E-LTP requires three trains (1 sec, once per min) of 100-Hz stimulation even in lowered magnesium (Colina and Malenka 1993; Nguyen and Kandel 1996).

In contrast to E-LTP, the late phase of LTP generally requires multiple trains of 100-Hz stimulation (1 sec duration). In the Schaffer collateral and mossy fiber pathways, L-LTP can be produced with 3–4 trains spaced 5–10 min apart (Frey et al. 1993; Huang and Kandel 1994; Huang et al. 1994; Nguyen et al. 1994). In the medial perforant pathway, where E-LTP requires three trains, L-LTP requires 10 trains given once per minute in the presence of lowered magnesium (Nguyen and Kandel 1996). The need for more tetanization in the dentate gyrus for both E-LTP and L-LTP presumably reflects the greater synaptic inhibition present in this region. Thus, L-LTP differs from E-LTP in requiring repeated tetanization with temporally spaced trains of stimulation eliciting particularly robust L-LTP.

As is evident in the other papers of this issue, much attention has focused on the early phase of LTP. In contrast, fewer studies have examined the mechanisms underlying the late phase of LTP. In the remainder of this review, we shall describe recent work designed to explore the molecular events involved in the induction and expression of L-LTP in hippocampal slices. We will focus in particular on three questions: Which signal transduction pathways are important for L-LTP? How is the switch from E-LTP to L-LTP achieved? and Which genes are important for the establishment of L-LTP?

The Cyclic-AMP Signal Transduction Pathway Is an Essential Component of the Late Phase of LTP

Cell biological studies of sensitization of the gill and siphon-withdrawal reflex in the marine snail *Aplysia californica* have revealed that both short-term and long-term facilitation of synaptic transmission between sensory and motor neurons involve cAMP and cAMP-dependent protein kinase (PKA; Ghirardi et al. 1992). A parallel requirement for PKA and cAMP has emerged in studies of short- and long-term memory in *Drosophila* (Kandel and Abel 1995). Does the cAMP pathway also play a role in memory storage in the mammalian brain? Specifically, is it important in mediating L-LTP in the hippocampus?

In the Schaffer collateral-CA1 pathway, application of Sp-cAMPS, a PKA activator, induces LTP lasting for several hours (Frey et al. 1993). This Sp-cAMPS-induced potentiation occluded L-LTP induced by repeated

tetanzation, and was blocked by anisomycin, a protein synthesis inhibitor. Furthermore, the PKA inhibitors Rp-cAMPS and KT-5720 (which act on the regulatory and catalytic subunits of PKA, respectively), blocked L-LTP when applied during tetanzation (Frey et al. 1993; Huang and Kandel 1994). These results support the idea that repeated tetanzation increases cAMP levels, thereby activating PKA. Indeed, depolarization and tetanzation are known to transiently increase cAMP levels in hippocampal slices (Chetkovich et al. 1991; Frey et al. 1993). Forskolin, an adenylate cyclase activator, can induce synaptic potentiation in area CA1, and this potentiation occludes L-LTP (Chavez-Noriega and Stevens 1992; Huang and Kandel 1994; Impey et al. 1996).

How is the cAMP pathway coupled to membrane depolarization? In area CA1, LTP is dependent upon NMDA receptor activation, and the influx of calcium through NMDA receptor channels (and voltage-gated calcium channels) can activate adenylate cyclase and raise cAMP levels (Chetkovich et al. 1991; Chetkovich and Sweatt 1993). Other membrane receptors coupled to adenylate cyclase, such as dopamine receptors, might also be important for L-LTP induction in CA1 region. Indeed, D1/D5 receptor antagonists selectively block L-LTP, whereas D1/D5 receptor agonists induce a potentiation that occludes L-LTP (Huang and Kandel 1995).

In the mossy fiber and the medial perforant pathways, cAMP and PKA also appear to be crucial for L-LTP induction. NMDA receptor-independent LTP in the mossy fiber pathway consists of an early phase and a late phase and both are blocked by inhibitors of PKA (Weisskopf et al. 1994; Huang et al. 1994). Forskolin and Sp-cAMPS induce long-lasting potentiation with the forskolin-induced potentiation occluding tetanzation-induced LTP (Huang et al. 1994). As in the Schaffer collateral pathway, modulating inputs have powerful effects. Thus, antagonists of beta-adrenergic receptors block both E-LTP and L-LTP in the mossy fiber pathway, suggesting that activation of cAMP-coupled β receptors can modulate L-LTP in this pathway (Huang and Kandel 1996). Medial perforant pathway L-LTP, but not E-LTP, was blocked by PKA inhibitors and simulated by forskolin (Nguyen and Kandel 1996). It has been suggested that norepinephrine may be involved in LTP in the perforant pathway (e.g. Stanton and Sarvey 1985). Thus, the pharmacological evidence suggests that cAMP and PKA are vital for induction of L-LTP in all three pathways (Fig. 1, 2).

Genetic Manipulation of the cAMP Signal Transduction Pathway

In addition to pharmacological blockade and activation of PKA and adenylate cyclase, recent studies utilizing gene targeting and transgenesis have yielded genetic evidence that the cAMP signal transduction pathway is important for L-LTP. In mice that lack the gene encoding the C β 1 catalytic subunit of PKA, L-LTP in area CA1 was deficient: mutant mice showed a late phase that was only 30% of controls (Qi et al. 1996). Similarly, overexpression of an inhibitory form of a regulatory subunit of PKA blocked expression of L-LTP in CA1, without affecting E-LTP. (T. Abel, P.V. Nguyen, and E.R. Kandel, unpubl.). In the mossy fiber pathway, genetic ablation of either the C β 1 or the RI β subunit of PKA attenuated both E-LTP and L-LTP (Huang et al. 1995b). These genetic studies show that PKA is critical for L-LTP. Other evidence implicating the cAMP/PKA signaling pathway in Schaffer collateral LTP comes from studies of mice lacking either adenylate cyclase (Wu et al. 1995) or CREB (cAMP

Figure 1: L-LTP in each synaptic pathway of the hippocampal trisynaptic circuit requires PKA activity, protein synthesis and RNA synthesis. (A) The PKA inhibitor KT5720 selectively blocks L-LTP induced by multiple tetanic trains in the Schaffer collateral (A₁) and perforant pathways (A₂). In the mossy fiber pathway, PKA is required for LTP induced by both single and multiple trains (A₃). (B) Protein synthesis is required for the full expression of L-LTP in each major hippocampal pathway. (C) The RNA synthesis inhibitor, actinomycin D, selectively blocks L-LTP in all three pathways. (D) Potentiation induced by activators of the PKA pathway also requires protein and mRNA synthesis. (Adapted from Huang and Kandel 1994; Huang et al. 1994; Nguyen and Kandel 1996.)

Huang et al.

Figure 2: Schematic model of the molecular mechanisms thought to underlie the early and late phases of LTP in hippocampal regions of CA1 and CA3. See text for details.

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response element binding protein; Bourtchouladze et al. 1994), although these studies did not attempt to distinguish specifically between E-LTP and L-LTP by use of various tetanization protocols.

Which proteins are acted upon by PKA during L-LTP? Because numerous substrates for PKA exist in neurons, including ion channels, neurotransmitter receptors, and transcription factors, it is likely that multiple target proteins are modified by PKA and play important roles in L-LTP. For example, AMPA receptor currents are enhanced during LTP, and AMPA-kainate receptors are phosphorylated by PKA (Greengard et al. 1991; Wang et al. 1991), resulting in increased activity. PKA may also act as a gate by regulating the activity of phosphoprotein phosphatases (Blitzer et al. 1995). The transcription factor CREB is also phosphorylated by PKA (Yamamoto et al. 1988) and is thought to participate in establishing the late phase of LTP (see below).

Gene Expression and Protein Synthesis Are Unique Requirements for the Late Phase of LTP in the Hippocampus

L-LTP differs from E-LTP in requiring both new protein synthesis and gene transcription. In all three regions of the hippocampus, time-restricted inhibition of protein synthesis blocks expression of the late phase of LTP (Frey et al. 1988, 1993; Huang et al. 1994; Nguyen and Kandel 1996; Fig. 1). When protein synthesis inhibitors are present during tetanization and field EPSPs are measured, LTP decays to baseline ~2–3 hr after induction (Otani et al. 1992; Huang and Kandel 1994; Huang et al. 1994; Nguyen and Kandel 1996; Osten et al. 1996). In contrast, E-LTP elicited with fewer trains is unaffected by protein synthesis inhibitors (Huang and Kandel 1994; Nguyen and Kandel 1996). Hence, activity-induced synthesis of new proteins is likely critical for expression of the late, but not the early, phase of hippocampal LTP. Indeed, LTP induction in dentate gyrus is accompanied by significant quantitative changes in protein synthesis occurring with a time course mirroring that of the late phase of LTP (Fazeli et al. 1993).

Because a requirement for protein synthesis often implies a need for gene transcription, we have also explored the role of RNA synthesis in L-LTP. Earlier studies have indicated that immediate-early gene induction and activity-dependent regulation of gene expression may be involved in LTP (e.g., Abraham et al. 1991; Qian et al. 1993; Hughes and Dragunow 1995). We have found that in the Schaffer collateral, mossy fiber, and perforant pathways (Huang et al. 1994; Nguyen et al. 1994; Nguyen and Kandel 1996; Fig. 1), inhibition of transcription blocked full expression of L-LTP without attenuating E-LTP. The time courses of decay of L-LTP in all three hippocampal regions were similar, with field EPSP slopes reaching near baseline values ~2–4 hr after tetanization (Huang et al. 1994; Nguyen et al. 1994; Nguyen and Kandel 1996).

These results with transcriptional inhibitors stand in contrast to those of Otani et al. (1989) and Frey et al. (1996). The former did not observe any significant effect of actinomycin-D on LTP induced in the dentate gyrus *in vivo*, while Frey et al. (1996) saw a delayed slight attenuation of L-LTP in CA1 with actinomycin-D (~6 hr after tetanization). The differences in results may be explained by variations in induction protocols and durations of drug application. Nonetheless, despite these differences in the time course of effects of transcriptional inhibition, gene transcription is essential for full, robust maintenance of L-LTP of field EPSPs in hippocampal slices.

Is the site of protein synthesis pre- or postsynaptic? A number of

studies point to the postsynaptic cells as one probable locus for activity-dependent changes in protein synthesis. First, blockade of protein synthesis in the dentate gyrus in vivo attenuated L-LTP, whereas inhibition in the entorhinal cortex (site of presynaptic cell bodies of perforant path axons) did not affect L-LTP (Otani and Abraham 1989). Second, electrical stimulation leading to potentiation induces a number of mRNAs and proteins in postsynaptic dentate granule cells, including tissue plasminogen activator (tPA) (Qian et al. 1993) and other immediate-early genes (Hughes and Dragunow 1995). Finally, it should be noted that in area CA1 of hippocampal slices, only a transient potentiation is present in postsynaptic CA1 dendrites that were severed from pyramidal cell bodies (Frey et al. 1989).

Which cAMP-inducible Genes are Critical for the Late Phase of LTP?

L-LTP in all three hippocampal regions can be simulated by activating adenylate cyclase using forskolin (Huang et al. 1994; Sarvey and Voulalas 1995; Nguyen and Kandel 1996; Impey et al. 1996) or by activating PKA with Sp-cAMPS (Schaffer collateral and mossy fiber pathways: Frey et al. 1993; Huang et al. 1994; Fig. 1). The potentiation induced by chemical activation of the cAMP signaling pathway was blocked by transcriptional and translational inhibitors (Frey et al. 1993; Huang et al. 1994; Nguyen et al. 1994; Nguyen and Kandel 1996; Fig. 1), suggesting that cAMP-inducible gene expression may underlie L-LTP.

Which cAMP-dependent genes contribute to L-LTP? Members of the CREB family of transcription factors activate the transcription of genes with CRE sequences in their promoter in response to increases in the intracellular concentration of cAMP. In *Aplysia*, there is clear evidence for the involvement of CREB and CREB-like transcriptional activators and repressors in long-term, but not short-term, facilitation (Dash et al. 1990; Kaang et al. 1993; Bartsch et al. 1995). In *Drosophila* as well, mutant flies that express a repressor of CREB show defective long-term memory for olfactory learning, with intact learning capabilities (Yin et al. 1994). In mice with a targeted disruption of two isoforms of CREB, long-term memory for fear conditioning and LTP were deficient. The maintenance of LTP induced in the Schaffer collateral pathway by one stimulus train was affected and basal synaptic transmission was enhanced. Other forms of synaptic plasticity, such as PTP and paired-pulse facilitation, were unchanged in the CREB knockout mice (Bourtchuladze et al. 1994). The disruption of CREB also leads to a selective deficit in the late phase of LTP in the mossy fiber pathway (T. Abel, Y.Y. Huang, and E.R. Kandel, unpubl.). L-LTP in mouse hippocampal area CA1 is accompanied by increased transcription from CREs (cAMP response elements) linked to a β -galactosidase reporter gene (Impey et al. 1996). Inhibitors of PKA blocked the L-LTP-associated increase of CRE-mediated gene expression.

The identities of the late effector gene products required for L-LTP are not yet known. One candidate gene is tissue plasminogen activator (tPA). tPA gene induction occurs following tetanization of the perforant pathway in rats (Qian et al. 1993) and after forskolin application (Baranes et al. 1995). Mice lacking tPA show reduced L-LTP in CA1 and CA3 and blunted responses to cAMP analogs (Frey et al. 1996; Huang et al. 1996). Moreover, recombinant t-tPA could stimulate the induction of L-LTP (Huang et al. 1995a). tPA deficient mice are resistant to neuronal degeneration and are less susceptible to drug-induced seizures (Tsirka et

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al. 1995). Hence, tPA could modulate and control cellular excitability and the molecular events underlying the growth and differentiation of new synaptic connections believed to occur during LTP (Bailey and Kandel 1993).

An Overall View

There is now good evidence that LTP in all three regions of the hippocampus has both an early and a late phase, and that the late phase involves new protein and RNA synthesis mediated by cAMP and PKA (Figs. 1, 2). As in *Aplysia*, long-term enhancement of transmitter release may involve a cAMP-inducible program of gene expression consisting of a cascade of early- and late-effector genes. That a similar basic mechanism for learning-related long-term synaptic facilitation exists in all three regions of the hippocampus (Fig. 2) attests to the notion that, although memory storage is distributed and involves several parallel pathways and different storage loci, the mechanisms used for converting short-term to long-term plasticity at these different sites may be conserved. This conservation may reflect the observation that long-term changes in synaptic strength are accompanied by structural changes (Bailey and Kandel 1993).

Although the temporal phases of LTP are now beginning to be delineated, we know little about the specific molecular steps underlying the late phase of LTP. Nor do we know the behavioral significance of L-LTP in each of the hippocampal regions. Some important questions that need to be explored include the following: First, what other signal transduction pathways are critical for L-LTP and long-term memory? PKA acting via CREB appears to be critical for L-LTP, but CREB is also a target protein for other signaling pathways besides cAMP. It can be activated by CaM kinase II and by various neurotrophins such as NGF and BDNF (Dash et al. 1991; Sheng et al. 1991; Ginty et al. 1994). BDNF appears to modulate synaptic transmission and short-term LTP in the Schaffer collateral pathway (Patterson et al. 1996), and it will be interesting to see whether neurotrophins also regulate the late phase of LTP. Second, are transcription factors other than CREB required for L-LTP and long-term memory? Does transcriptional repression, perhaps by CREB-2 (ATF4), play a critical role in the transition from short-term to long-term LTP in the hippocampus as during long-term facilitation in *Aplysia* (Bartsch et al. 1995)? Are the cellular and molecular mechanisms responsible for long-term changes lasting hours in hippocampal slices also important for the storage of memories that last for months or years? Finally, are structural changes evident during L-LTP, and how might these morphological transformations translate into the persistence of enhanced transmitter release and long-term memory? With the help of molecular genetics to resolve these questions, it may soon be possible to obtain answers that will bridge the fields of neurophysiology, molecular biology, and cognitive psychology and provide clues to understanding how organisms, including ourselves, remember events for long periods of time.

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