spatial memory by encoding a representation of an animal's location in its environment.

Explicit Memory in Mammals Involves Synaptic Plasticity in the Hippocampus

Unlike working memory, which is thought to be maintained by ongoing neural activity in the prefrontal cortex (Chapter 52), the long-term storage of information is thought to depend on long-lasting changes in the strength of connections among specific ensembles of neurons (neural assemblies) in the hippocampus that encode particular elements of memory.

The idea that memory storage involves long-lasting structural changes in the brain, first referred to as an "engram" by the German biologist Richard Semon in the early 20th century, dates back to the French philosopher Rene Descartes. In an attempt to locate an engram, the American psychologist Karl Lashley examined the effects of lesions in different regions of the neocortex on the ability of a rat to learn to navigate a maze. Since the performance in the maze seemed to be directly proportional to the size of the lesion, rather than its precise location, Lashley concluded that any memory trace must be distributed throughout the brain. Although it is now generally accepted that storage of an explicit memory is distributed throughout the neocortex, it is also clear that the process of storing memory requires the hippocampus, as demonstrated by the pioneering studies of Brenda Milner on patient H.M. (Chapter 52) and subsequent studies in animals with targeted lesions of the hippocampus. Thus, understanding how the brain stores explicit memory depends on an understanding of how the cortico-hippocampal circuit processes and stores information.

The nature of the basic mechanisms for memory storage was and remains the subject of much speculation and debate among psychologists and neuroscientists. One influential theory was proposed by the Canadian psychologist Donald Hebb, who suggested in 1949 that memory-encoding neural assemblies may be generated when synaptic connections are strengthened based on experience. According to *Hebb's rule*: "When an axon of cell A . . . excites cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells so that A's efficiency as one of the cells firing B is increased." The key element of Hebb's rule is the requirement for coincidence of pre- and postsynaptic firing, and so the rule has sometimes been rephrased as "Cells that fire together, wire together." A similar Hebbian coincidence principle is thought to be involved in fine-tuning synaptic connections during the late stages of development (Chapter 49). Hebb's ideas were later refined by the theoretical neuroscientist David Marr, based on a consideration of the hippocampal circuit.

The hippocampus comprises a loop of connections that process multimodal sensory and spatial information from the superficial layers of the nearby entorhinal cortex. This information passes through multiple synapses before arriving at the hippocampal CA1 region, the major output area of the hippocampus. The critical importance of CA1 neurons in learning and memory is seen in the profound memory loss exhibited by patients with lesions in this region alone, an observation supported by numerous animal studies. Information from the entorhinal cortex reaches CA1 neurons along two excitatory pathways, one direct and one indirect.

In the indirect pathway, the axons of neurons in layer II of the entorhinal cortex project through the *perforant pathway* to excite the granule cells of the dentate gyrus (an area considered part of the hippocampus). Next, the axons of the granule cells project in the *mossy fiber pathway* to excite the pyramidal cells in the CA3 region of the hippocampus. Finally, axons of the CA3 neurons project through the *Schaffer collateral pathway* to make excitatory synapses on more proximal regions of the dendrites of the CA1 pyramidal cells (Figure 54–1). (Because of its three successive excitatory synaptic connections, the indirect pathway is often referred to as the *trisynaptic pathway*). Finally, CA1 pyramidal cells project back to the deep layers of entorhinal cortex and forward to the subiculum, another medial temporal lobe structure that connects the hippocampus with a wide diversity of brain regions.

In parallel with the indirect pathway, the entorhinal cortex also projects directly to CA3 and CA1 hippocampal regions. In the direct pathway to CA1, neurons in layer III of the entorhinal cortex send their axons through the *perforant pathway* to form excitatory synapses on the very distal regions of the apical dendrites of CA1 neurons (such projections are also called the *temporoammonic pathway*). Interactions between direct and indirect inputs at each stage of the hippocampal circuit are likely important for memory storage or recall, although the precise nature of these interactions remains to be determined.

In addition to the above pathways that link different stages of the hippocampal circuit, CA3 pyramidal neurons also make strong excitatory connections with one another. This self-excitation through recurrent collaterals is thought to contribute to associative aspects of memory storage and recall. Under pathological conditions, such self-excitation can lead to seizures.

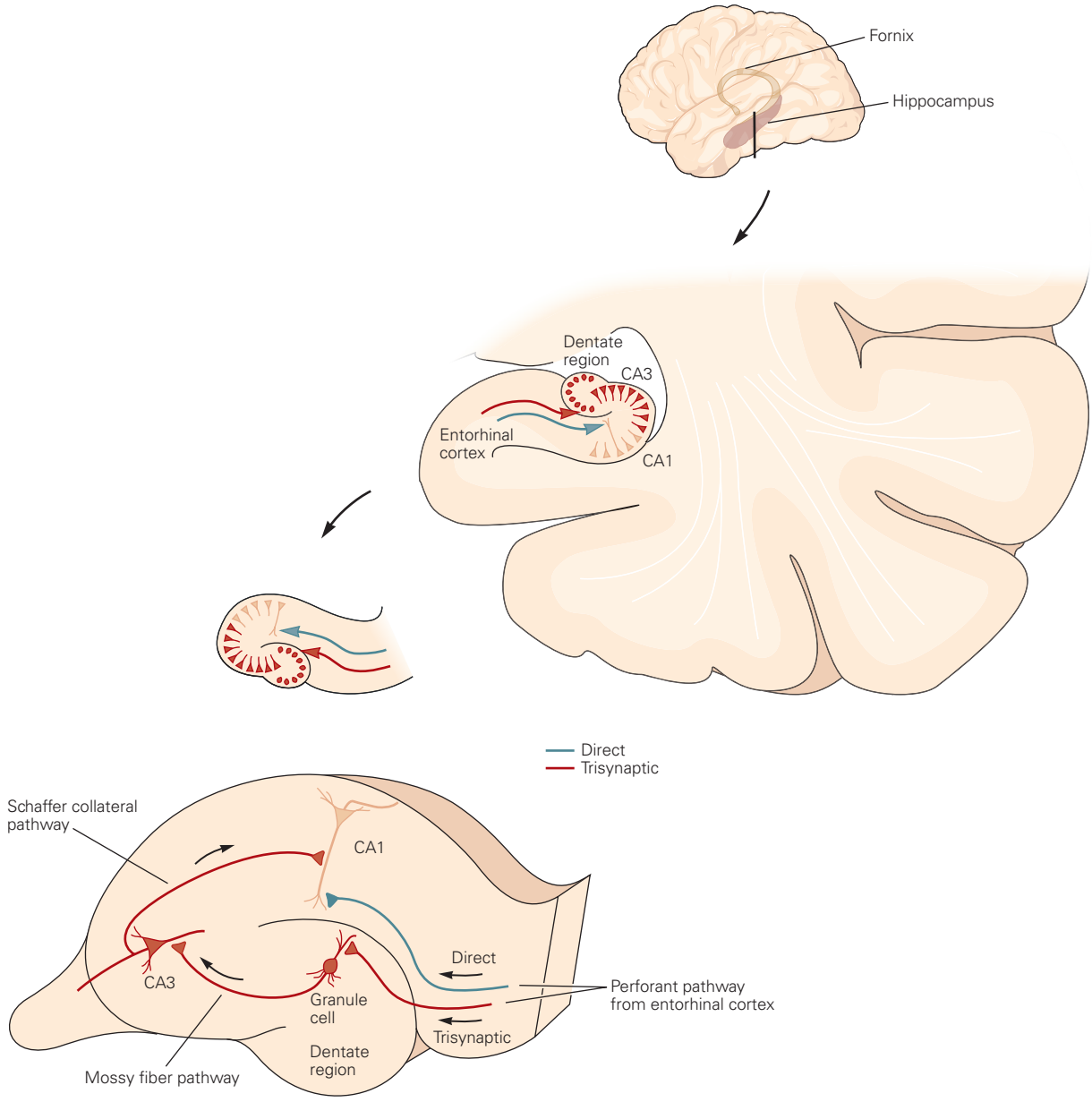


Figure 54–1 The cortico-hippocampal synaptic circuit is important for declarative memory. Information arrives in the hippocampus from the entorhinal cortex through the perforant pathways, which provide both direct and indirect input to pyramidal neurons in area CA1, the major output neurons of the hippocampus. (**Arrows** denote the direction of impulse flow.) The indirect *trisynaptic pathway* has three component connections. Neurons in layer II of the entorhinal cortex send their axons through the perforant path to make excitatory synapses onto the granule cells of the dentate gyrus. The granule cells project through the mossy fiber pathway and make excitatory synapses with the pyramidal cells in area CA3 of the hippocampus. The CA3 cells excite the pyramidal cells in CA1 by means of the Schaffer collateral pathway. In the *direct pathway*, neurons in layer III of the entorhinal cortex project through the perforant path to make excitatory synapses on the distal dendrites of CA3 and CA1 pyramidal neurons without inter vening synapses (shown only for CA1).

Finally, neurons in the relatively small CA2 region, located between CA3 and CA1, receive information from entorhinal cortex layer II through both a direct pathway and an indirect pathway via the dentate gyrus and CA3. The CA2 region also receives strong input from hypothalamic nuclei that release oxytocin and vasopressin, hormones important for social behavior. In turn, CA2 sends a strong output to CA1,

providing CA1 with a third source of excitatory input (in addition to the direct and trisynaptic routes from the entorhinal cortex).

Long-Term Potentiation at Distinct Hippocampal Pathways Is Essential for Explicit Memory Storage

How is information stored in the hippocampal circuit to provide a long-lasting memory trace? In 1973, Timothy Bliss and Terje Lømo discovered that a brief period of high-frequency synaptic stimulation causes a persistent increase in the amplitude of hippocampal excitatory postsynaptic potentials (EPSPs), a process termed *long-term potentiation* or LTP (Chapter 13). The enhancement in the EPSP, in turn, increases the probability that the postsynaptic cell will fire action potentials.

Bliss and Lømo examined the initial stage of the indirect hippocampal pathway—the synapses formed by the perforant pathway from entorhinal cortex layer II neurons with dentate gyrus granule neurons. Subsequent studies showed that brief high-frequency trains of stimulation can induce forms of LTP at nearly all excitatory synapses of this indirect pathway as well as at the direct perforant path synapses with CA3 and CA1 neurons (Figure 54–2). LTP can last for days or even weeks when induced in intact animals using implanted electrodes and can last several hours in isolated slices of hippocampus and in hippocampal neurons in cell culture.

Studies in the different hippocampal pathways have shown that LTP at different synapses is not a single process. Rather, it comprises a family of processes that strengthen synaptic transmission at different hippocampal synapses through distinct cellular and molecular mechanisms. Indeed, even at a single synapse, different forms of LTP can be induced by different patterns of synaptic activity, although these distinct processes share many important similarities.

All forms of LTP are induced by synaptic activity in the pathway that is being potentiated—that is, LTP is homosynaptic. In addition, LTP is synapse specific; only those synapses that are activated by the tetanic stimulation are potentiated. However, the various forms of LTP differ in their dependence on specific receptors and ion channels. In addition, different forms of LTP recruit different second-messenger signaling pathways that act at different synaptic sites. Some forms of LTP result from an enhancement of the postsynaptic response to the neurotransmitter glutamate, whereas other forms of LTP result from the enhancement of glutamate release from the presynaptic terminal, and still other forms of LTP engage both the presynaptic and postsynaptic neurons.

The similarities and differences in the mechanisms of different forms of LTP can be seen by comparing LTP at Schaffer collateral, mossy fiber, and direct entorhinal synapses. In all three pathways, synaptic transmission is persistently enhanced in response to a brief tetanic stimulation. However, the contribution of the *N*-methyl-D-aspartate (NMDA) receptor to the induction of LTP differs in the three pathways. At the Schaffer collateral synapses, the induction of LTP in response to a brief 100-Hz stimulation is completely blocked when the tetanus is applied in the presence of the NMDA receptor antagonist 2-amino-5-phosphonovaleric acid (AP5 or APV). In contrast, APV only partially inhibits the induction of LTP at the direct entorhinal synapses with CA1 neurons and has no effect on LTP at the mossy fiber synapses with CA3 pyramidal neurons (Figure 54–2).

Long-term potentiation in the mossy fiber pathway is largely presynaptic and is triggered by the large Ca^{2+} influx into the presynaptic terminals during the tetanus. The Ca^{2+} influx activates a calcium/calmodulin-dependent adenylyl cyclase, thereby increasing the production of cyclic adenosine monophosphate (cAMP) and activating protein kinase A (PKA; see Chapter 14). This leads to the phosphorylation of presynaptic vesicle proteins that enhance the release of glutamate from the mossy fiber terminals, resulting in an increase in the EPSP. Activity in the postsynaptic cell is not required for this form of LTP. Thus, unlike Hebbian plasticity, mossy fiber LTP is nonassociative.

In the Schaffer collateral pathway, however, LTP is associative, largely as a result of the properties of the NMDA receptors (Figure 54–3; see also Chapter 13). As is the case with most excitatory synapses in the brain, glutamate released from the Schaffer collateral terminals activates both α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and NMDA receptor-channels in the postsynaptic membrane of CA1 pyramidal neurons. However, unlike the AMPA receptors, activation of the NMDA receptors is associative because it requires simultaneous presynaptic and postsynaptic activity. This is because the pore of the NMDA receptor-channel is normally blocked by extracellular Mg^{2+} at typical negative resting potentials, which prevents these channels from conducting ions in response to glutamate. For the NMDA receptor-channel to function efficiently, the postsynaptic membrane must be depolarized sufficiently to expel the bound Mg^{2+} by electrostatic repulsion. In this manner, the NMDA receptor-channel acts as a coincidence detector: It is functional only when (1) the action potentials in the presynaptic neuron release glutamate that binds to the receptor *and* (2) the membrane of the postsynaptic

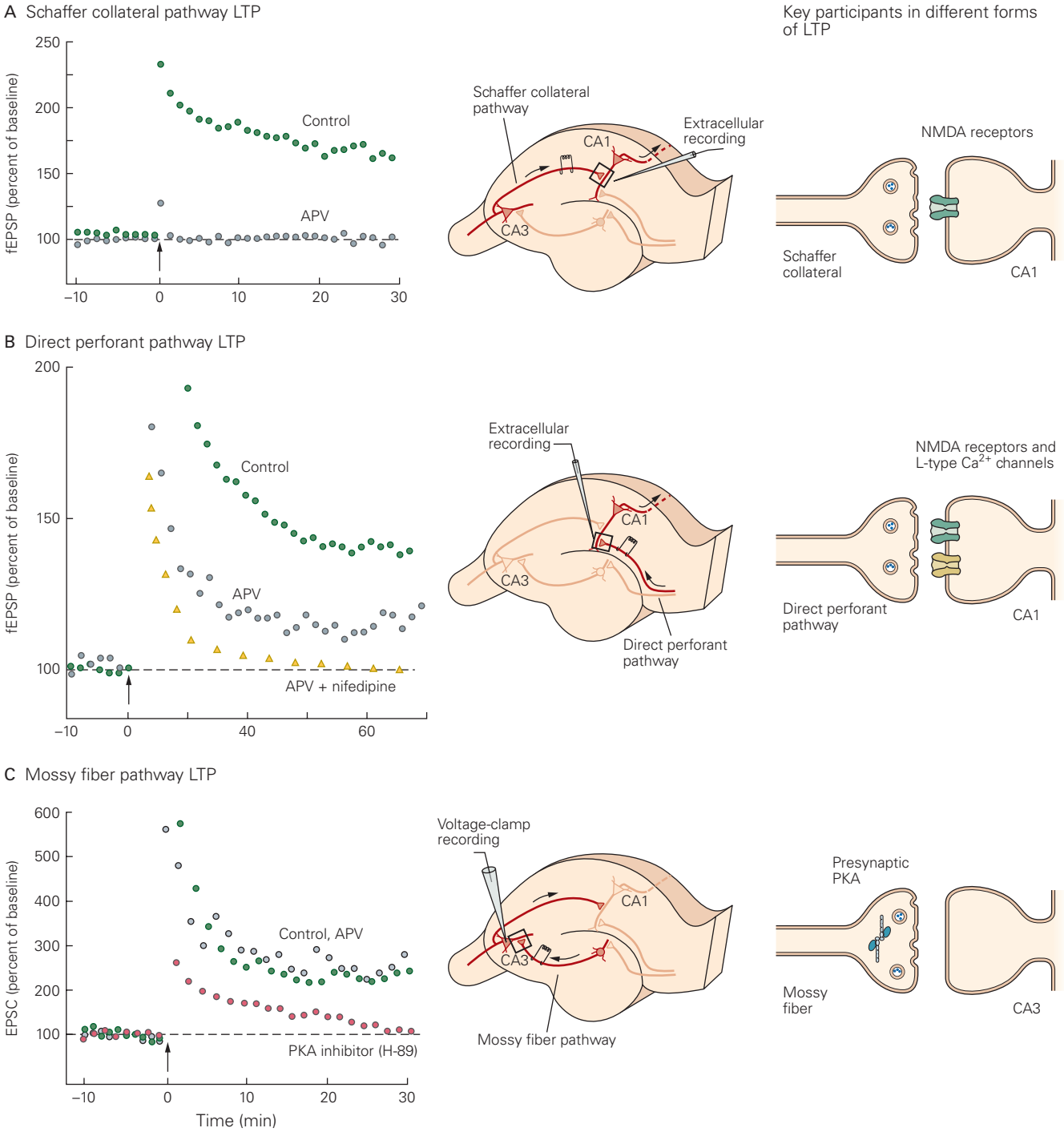
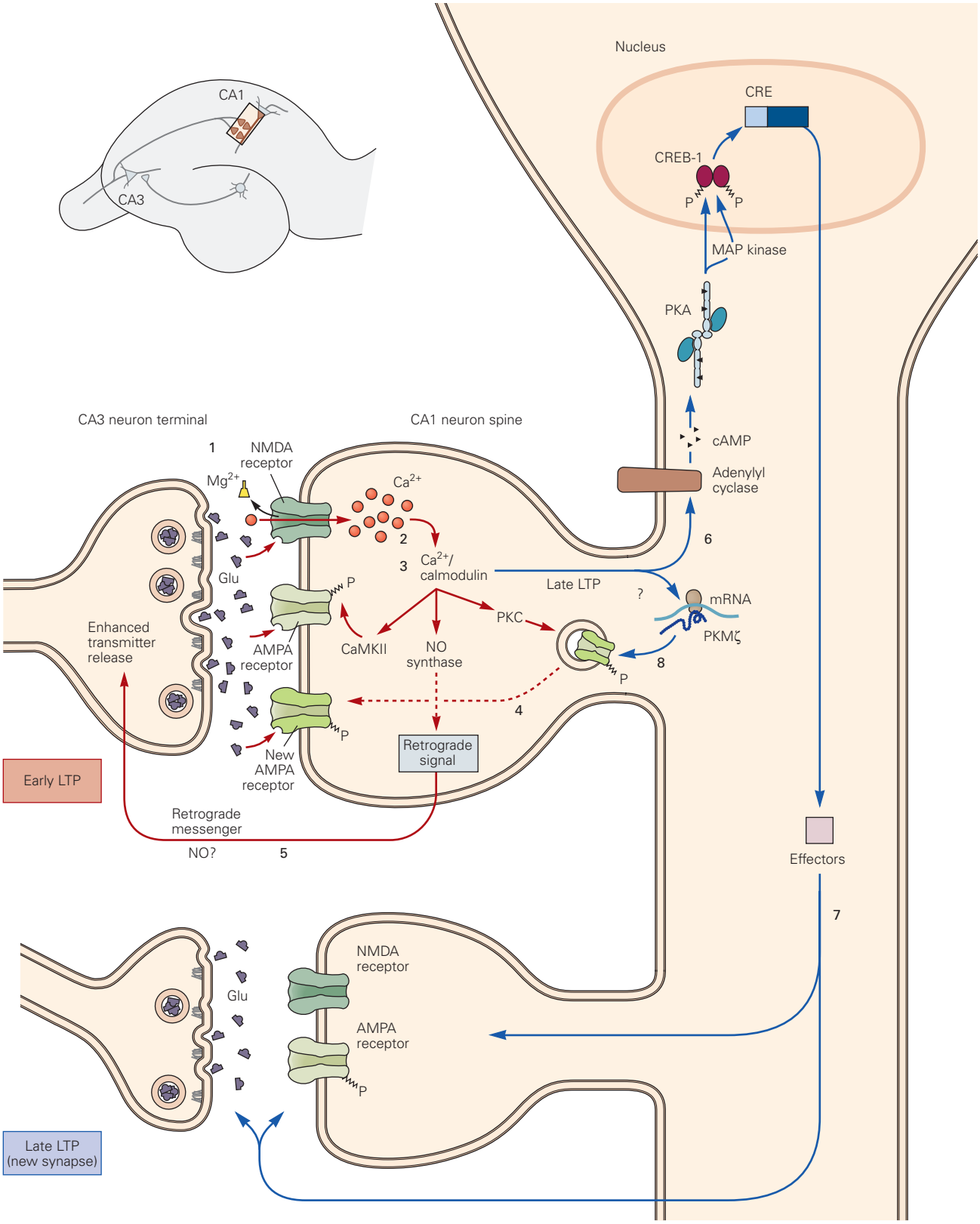


Figure 54–2 Different neural mechanisms underlie long-term potentiation at each of the three synapses in the trisynaptic pathway. Long-term potentiation (**LTP**) occurs at synapses throughout the hippocampus but depends to differing degrees on activation of *N*-methyl-D-aspartate (**NMDA**)-type glutamate receptors.

A. Tetanic stimulation of the Schaffer collateral fibers (at time 0 in the plot) induces LTP at the synapses between presynaptic CA3 pyramidal neurons and postsynaptic CA1 pyramidal neurons. The plot shows the size of the extracellular field excitatory postsynaptic potential (**fEPSP**) as a percentage of the baseline fEPSP prior to induction of LTP. At these synapses, LTP requires activation of the NMDA receptor-channels in the postsynaptic CA1 neurons as it is completely blocked when the tetanus is delivered in the presence of the NMDA receptor antagonist 2-amino-5-phosphonovaleric acid (**APV**). (Adapted from Morgan and Teyler 2001.)

B. Tetanic stimulation of the direct pathway from entorhinal cortex to CA1 neurons generates LTP of the fEPSP that depends partly on activation of the NMDA receptor-channels and partly on activation of L-type voltage-gated Ca^{2+} channels. It is therefore only partially blocked by APV. Addition of APV and nifedipine, a dihydropyridine that blocks L type channels, is needed to fully inhibit LTP.

C. Tetanic stimulation of the mossy fiber pathway induces LTP at the synapses with the pyramidal cells in the CA3 region. In this experiment, the excitatory postsynaptic current (**EPSC**) was measured under voltage-clamp conditions. This LTP does not require activation of the NMDA receptors and so is not blocked by APV. However, it does require activation of protein kinase A (**PKA**) and so is blocked by the kinase inhibitor H-89. (Reproduced, with permission, from Zalutsky and Nicoll 1990. Copyright © 1990 AAAS.)


CA1
CA3
Nucleus
CRE
CREB-1
P
P
MAP kinase
PKA
cAMP
Adenylyl cyclase
CA3 neuron terminal
CA1 neuron spine
1
NMDA receptor
Mg^{2+}
Ca^{2+}
2
3
Ca^{2+}/ calmodulin
Late LTP
?
mRNA
PKMζ
6
Glu
P
Enhanced transmitter release
AMPA receptor
CaMKII
NO synthase
PKC
8
P
4
P
New AMPA receptor
Retrograde signal
Early LTP
Retrograde messenger
NO?
5
Effectors
7
Glu
NMDA receptor
AMPA receptor
P
Late LTP (new synapse)

cell is sufficiently depolarized by strong synaptic activity to relieve the Mg^{2+} block. Thus, the NMDA receptor is able to associate presynaptic and postsynaptic activity to recruit plasticity mechanisms that strengthen connections between pairs of cells, fulfilling Hebb's coincidence requirement for synaptic modification.

What are the functional consequences of the activation of NMDA receptors by strong synaptic excitation? Whereas most AMPA receptor-channels conduct only monovalent cations (Na^+ and K^+), the NMDA receptor-channels have a high permeability to Ca^{2+} (Chapter 13). Thus, the opening of these channels leads to a significant increase in the Ca^{2+}concentration in the postsynaptic cell. The increase in intracellular Ca^{2+} activates several downstream signaling pathways—including calcium/calmodulin–dependent protein kinase II (CaMKII), protein kinase C (PKC), and tyrosine kinases—that lead to changes that enhance the magnitude of the EPSP at Schaffer collateral synapses (Figure 54–3).

Different Molecular and Cellular Mechanisms Contribute to the Forms of Expression of Long-Term Potentiation

Neuroscientists often find it useful to distinguish between the *induction* of LTP (the biochemical reactions activated by the tetanic stimulation) and the *expression* of LTP (the long-term changes responsible for enhanced synaptic transmission). The mechanisms for the induction of LTP at the CA3-CA1 synapse are largely postsynaptic. Is the expression of LTP at this synapse caused by an increase in transmitter release, an increased postsynaptic response to a fixed amount of transmitter, or some combination of the two?

A number of lines of experiments suggest that the form of expression of LTP depends on the type of synapse and precise pattern of activity that induces LTP. In many cases, the expression of LTP in CA1 neurons in response to Ca^{2+} influx through NMDA receptor-channels depends on an increase in the response of the postsynaptic membrane to glutamate. But stronger patterns of stimulation can elicit forms of LTP at the same synapse whose expression depends on presynaptic events that enhance transmitter release.

One of the key pieces of evidence for a postsynaptic contribution to the expression of LTP at Schaffer collateral synapses comes from an examination of so-called "silent synapses." In some recordings from pairs of hippocampal pyramidal neurons, stimulation of an action potential in one neuron fails to elicit a response in the postsynaptic neuron when that neuron is at its resting potential (approximately –70 mV). This result is not surprising, as each hippocampal presynaptic neuron is connected to only a small number of other neurons. What *is* surprising is that in some neuronal pairs that appear unconnected when the postsynaptic membrane is initially at –70 mV, stimulation of the same presynaptic neuron is able to elicit a large excitatory postsynaptic current in the second neuron when the second neuron is depolarized under voltage clamp to +30 mV. In such neuronal pairs, the postsynaptic membrane appears to lack functional AMPA receptors so that the excitatory postsynaptic current (EPSC) is mediated solely by NMDA receptors-channels. As a result, there is no measurable EPSC when the membrane is held at the cell's resting potential (–70 mV) because of the strong Mg^{2+} block of these receptor-channels (the synapse is effectively silent). However, a large EPSC can be generated at +30 mV because the depolarization relieves the block (Figure 54–4).

The key finding from these experiments is seen following the induction of LTP using strong synaptic stimulation. Pairs of neurons initially connected solely by silent synapses now often exhibit large EPSPs at the

Figure 54–3 (Opposite) A model for the induction of long-term potentiation (LTP) at Schaffer collateral synapses. A single high-frequency tetanus induces early LTP. The large depolarization of the postsynaptic membrane (caused by strong activation of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid [**AMPA**] receptors) relieves the Mg^{2+} blockade of the *N*-methyl-D-aspartate (**NMDA**) receptor-channels (**1**), allowing Ca^{2+}, Na^+, and K^+ to flow through these channels. The resulting increase of Ca^{2+} in the dendritic spine (**2**) triggers calcium-dependent kinases (**3**)—calcium/calmodulin–dependent kinase (**CaMKII**) and protein kinase C (**PKC**)—leading to induction of LTP. Second-messenger cascades activated during induction of LTP have two main effects on synaptic transmission. Phosphorylation through activation of protein kinases, including PKC, enhances current through the AMPA receptor-channels, in part by causing insertion of new receptors into the spine synapses (**4**). In addition, the postsynaptic cell releases retrograde messengers, such as nitric oxide (**NO**), that activate protein kinases in the presynaptic terminal to enhance subsequent transmitter release (**5**). Repeated bouts of tetanic stimulation induce late LTP. The prolonged increase in Ca^{2+} influx recruits adenylyl cyclase (**6**), which generates cyclic adenosine monophosphate (**cAMP**) that activates protein kinase A (**PKA**). This leads to the activation of MAP kinase, which translocates to the nucleus where it phosphorylates CREB-1. CREB-1 in turn activates transcription of targets (containing the CRE promoter) that are thought to lead to the growth of new synaptic connections (**7**). Repeated stimulation also activates translation of mRNA encoding PKMζ, a constitutively active isoform of PKC (**8**). This leads to a long-lasting increase in the number of AMPA receptors in the postsynaptic membrane.

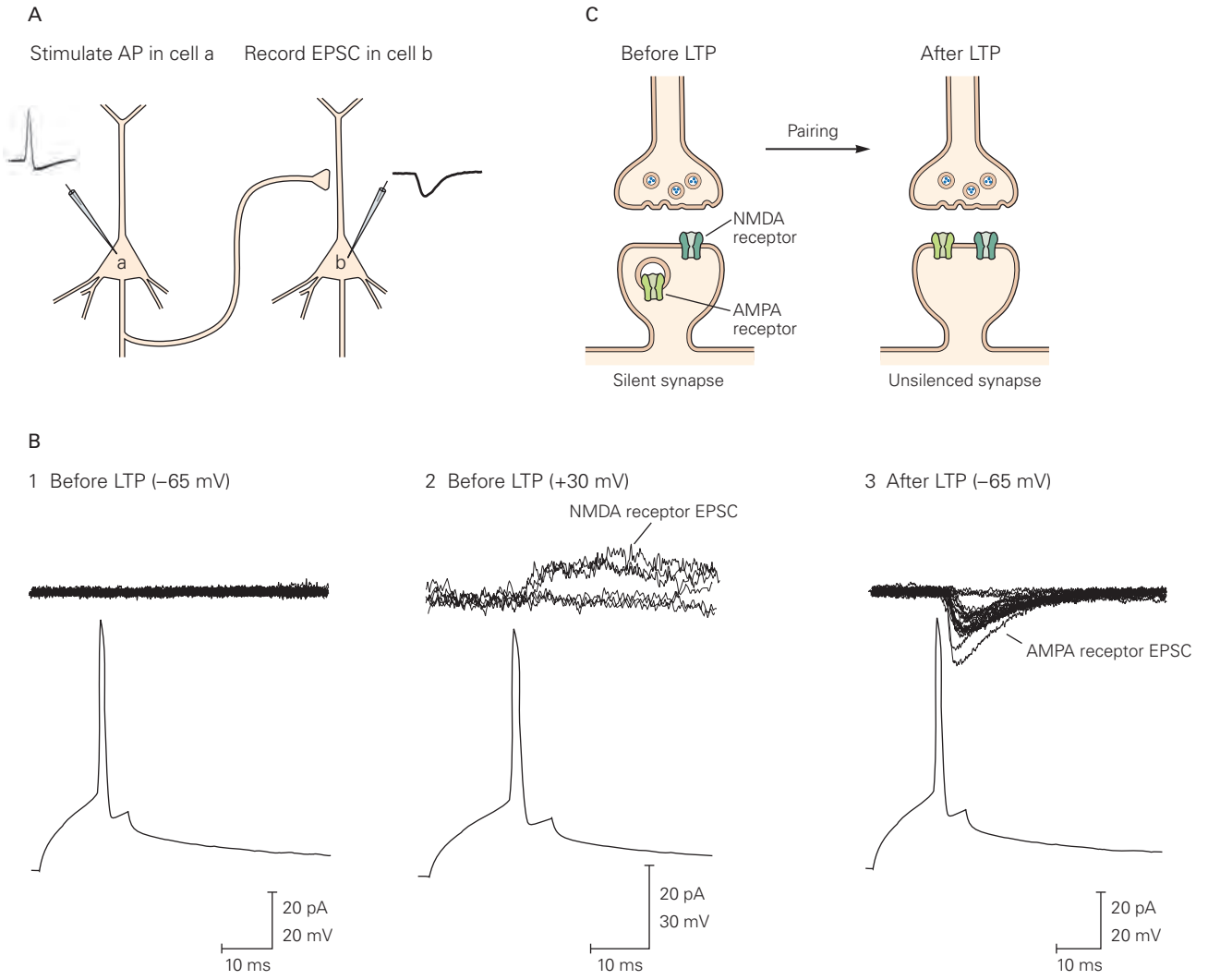


Figure 54–4 Adding α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors to silent synapses during long-term potentiation (LTP).

A. Intracellular recordings are obtained from a pair of hippocampal pyramidal neurons. An action potential (**AP**) is triggered in neuron *a* by a depolarizing current pulse, and the resultant excitatory postsynaptic current (**EPSC**) produced in neuron *b* is recorded under voltage-clamp conditions.

B. Before induction of LTP, there is no EPSC in cell *b* (top traces) in response to an action potential in cell *a* (bottom traces) when the membrane potential of neuron *b* is at its resting value of –65 mV (**1**). However, when neuron *b* is depolarized by the voltage clamp to +30 mV, the *N*-methyl-D-aspartate (**NMDA**) receptors are activated and slow EPSCs characteristic of these receptors are observed (**2**). LTP is then induced by pairing action potentials in neuron *a* with postsynaptic depolarization in neuron *b* to relieve the Mg^{2+} block of the NMDA receptors. After this pairing, fast EPSCs initiated by activation of AMPA receptors are seen in cell *b* (**3**). (Reproduced, with permission, from Montgomery, Pavlidis, and Madison 2001. Copyright © 2001 Cell Press.)

C. Mechanism of the unsilencing of silent synapses. Prior to LTP, the dendritic spine contacted by a presynaptic CA3 neuron contains only NMDA receptors. Following induction of LTP, intracellular vesicles containing AMPA receptors fuse with the plasma membrane at the synapse, adding AMPA receptors to the membrane.

negative resting potential, and these EPSPs are mediated by AMPA receptors. The simplest interpretation of this result is that LTP somehow recruits new functional AMPA receptors to the silent synapse membrane, a process Roberto Malinow refers to as "AMPAfication."

How does the induction of LTP increase the response of AMPA receptors? The strong synaptic stimulation used to induce LTP triggers glutamate release at both silent and nonsilent synapses on the same postsynaptic neuron. This leads to the opening

of a large number of AMPA receptor-channels at the nonsilent synapses, which in turn produces a large postsynaptic depolarization. The depolarization then propagates throughout the neuron, thus relieving Mg^{2+} block of the NMDA receptor-channels at both the nonsilent and silent synapses. At the silent synapses, the Ca^{2+} influx through the NMDA receptor-channels activates a biochemical cascade that ultimately leads to the insertion of clusters of AMPA receptors in the postsynaptic membrane. These newly inserted AMPA receptors are thought to come from a reserve pool stored in endosomal vesicles within dendritic spines, the site of all excitatory input to pyramidal neurons (Chapter 13). Calcium influx through the NMDA receptor-channels elevates spine Ca^{2+} levels, triggering a postsynaptic signaling cascade that leads to phosphorylation of the cytoplasmic tail of the vesicular AMPA receptors by PKC (Chapter 14), leading to their insertion in the postsynaptic membrane (Figure 54–3).

Because the induction of almost all forms of postsynaptic LTP requires Ca^{2+} influx into the postsynaptic cell, the finding that transmitter release is enhanced during some forms of LTP implies that the presynaptic cell must receive a signal from the postsynaptic cell that LTP has been induced. There is now evidence that calcium-activated second messengers in the postsynaptic cell, or perhaps Ca^{2+} itself, cause the postsynaptic cell to release one or more chemical messengers, including the gas nitric oxide, that diffuse to the presynaptic terminals to enhance transmitter release (Figure 54–3 and Chapter 14). Importantly, these diffusible retrograde signals appear to affect only those presynaptic terminals that have been activated by the tetanic stimulation, thereby preserving synapse specificity.

Long-Term Potentiation Has Early and Late Phases

Long-term potentiation has two phases, early and late, that provide a means of regulating the duration of the enhancement of synaptic transmission. The phase we have focused on up to now lasts for only 1 to 3 hours and is termed early LTP; this phase is typically induced by a single train of 100-Hz tetanic stimulation for 1 second. More prolonged periods of activity (using three or four trains of 100-Hz tetanic stimulation, each lasting 1 second) induce a late phase of LTP that can last 24 hours or even longer. Unlike early LTP, late LTP requires the synthesis of new proteins (Figure 54–5).

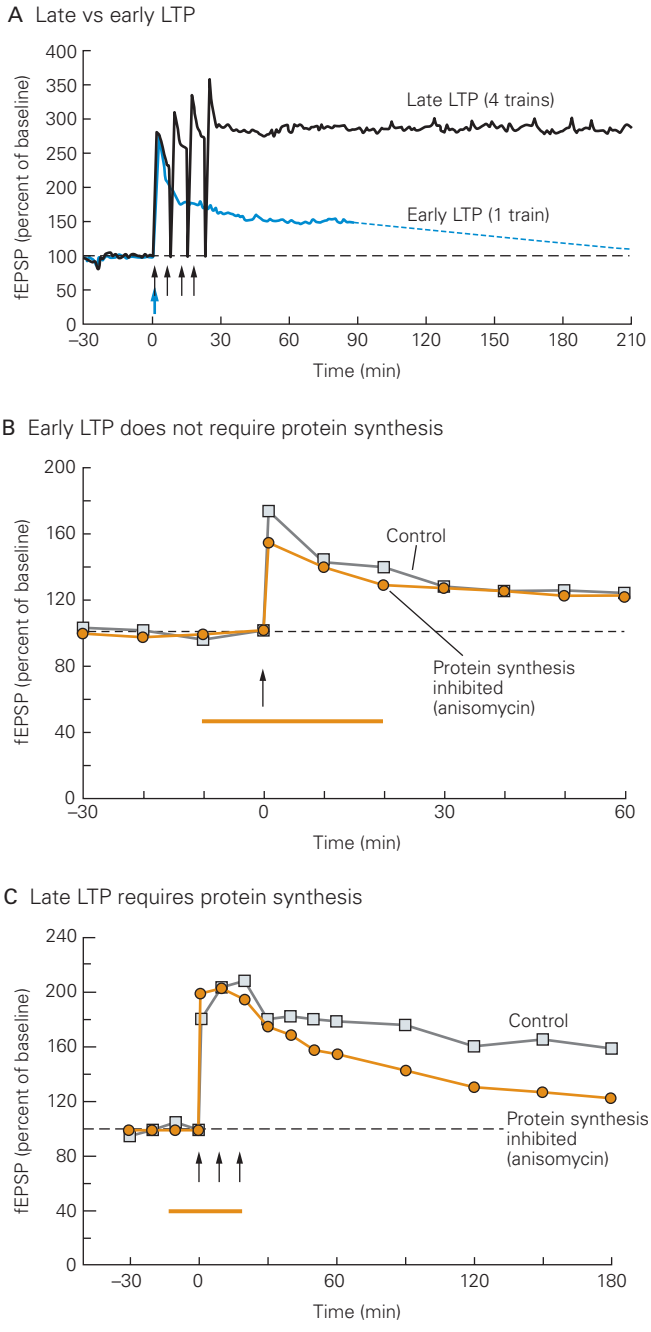


Figure 54–5 (Right) Long-term potentiation (LTP) in the CA1 region of the hippocampus has early and late phases.

A. Early LTP is induced by a single tetanus lasting 1 second at 100 Hz, whereas late LTP is induced by four tetani given 10 minutes apart. Early LTP of the field excitatory postsynaptic potential (**fEPSP**) lasts only 1 to 2 hours, whereas the late LTP lasts more than 8 hours (only the first 3.5 hours are shown).

B. Early LTP induced by one tetanus is not blocked by anisomycin (**bar**), an inhibitor of protein synthesis.

C. Late LTP, normally induced by three trains of stimulation, is blocked by anisomycin. (Three or four trains can be used to induce late LTP.) (Panels B and C reproduced, with permission, from Huang and Kandel 1994.)

Whereas the early phase of LTP is mediated by changes at existing synapses, late LTP is thought to result from the growth of new synaptic connections between pairs of co-activated neurons.

Although the mechanisms for early LTP in the Schaffer collateral and mossy fiber pathways are quite different, the mechanisms for late LTP in the two pathways appear similar (Figure 54–3). In both pathways, late LTP recruits the cAMP and PKA signaling pathway to activate by phosphorylation the cAMP response element binding protein (CREB) transcription factor, leading to the synthesis of new mRNAs and proteins. Like sensitization of the gill-withdrawal reflex in *Aplysia*, which also involves cAMP, PKA, and CREB (Chapter 53), late LTP in the Schaffer collateral pathway is synapse specific. When two independent sets of synapses in the same postsynaptic CA1 neuron are stimulated using two electrodes spaced some distance apart, the application of four trains of tetanic stimulation to one set of synapses induces late LTP only at the activated synapses; synaptic transmission is not altered at the second set of synapses that were not tetanized.

How can late LTP achieve synapse specificity given that transcription and most translation occurs in the cell body, such that newly synthesized proteins should be available to all synapses of a cell? To explain synapse specificity, Uwe Frey and Richard Morris proposed the synaptic capture hypothesis, in which synapses that are activated during the tetanus are tagged in some way, perhaps by protein phosphorylation, that enables them to make use of ("capture") the newly synthesized proteins. Frey and Morris tested this idea using the two-pathway protocol described above. They delivered four tetani to induce late LTP at one set of synapses with one electrode and delivered a single tetanus to a second set of synapses with the other electrode. Although a single tetanus on its own induces only early LTP, it is able to induce late LTP when delivered within 2–3 hours of the four tetani from the first electrode. This phenomenon is similar to the synapse-specific capture of long-term facilitation at the sensory-motor neuron synapses in *Aplysia* (Chapter 53).

According to Frey and Morris, the single train of tetanic stimulation, although not sufficient to induce new protein synthesis, is sufficient to tag the activated synapses, allowing them to capture the newly synthesized proteins produced in response to the prior delivery of the four trains of tetanic stimulation. The increased synaptic plasticity that this tagging mechanism affords, and its limitation to the period when newly synthesized proteins are around, may explain the recent finding that hippocampal cell assemblies that store memories of events closely spaced in time have a larger number of common neurons than do cell assemblies for events widely separated in time.

How can a few brief trains of synaptic stimulation produce such long-lasting increases in synaptic transmission? One mechanism proposed by John Lisman depends on the unique properties of CaMKII. After a brief exposure to Ca^{2+}, CaMKII can be converted to a calcium-independent state through its autophosphorylation at threonine-286 (Thr286). This ability to become persistently active in response to a transient Ca^{2+} stimulus has led to the suggestion that CaMKII may act as a simple molecular switch that can extend the duration of LTP following its initial activation.

Studies from Todd Sacktor have suggested that longer-lasting changes that maintain late LTP may depend on an atypical isoform of PKC termed PKMζ (PKM zeta). Most isoforms of PKC contain both a regulatory domain and a catalytic domain (Chapter 14). Binding of diacylglycerol, phospholipids, and Ca^{2+} to the regulatory domain relieves inhibitory domain binding to the catalytic domain, allowing PKC to phosphorylate its protein substrates. In contrast, PKMζ lacks a regulatory domain and so is constitutively active.

Levels of PKMζ in the hippocampus are normally low. Tetanic stimulation that induces LTP leads to an increase in synthesis of PKMζ through enhanced translation of its mRNA. Because this mRNA is present in the CA1 neuron dendrites, its translation can rapidly alter synaptic strength. Blockade of PKMζ with a peptide inhibitor during the tetanic stimulation blocks late LTP but not early LTP. If the blocker is applied several hours after LTP induction, the late LTP that had been established will be reversed. This result indicates that the maintenance of late LTP requires the ongoing activity of PKMζ to maintain the increase in AMPA receptors in the postsynaptic membrane (Figure 54–3). A second atypical PKC isoform may substitute for PKMζ under certain conditions, which may explain the surprising finding that genetic deletion of PKMζ has little effect on late LTP.

Constitutively active forms of protein kinases may not be the only mechanism for maintaining long-lasting synaptic changes in the hippocampus. Repeated stimulation may lead to the formation of new synaptic connections, just as long-term facilitation leads to the formation of new synapses during learning in *Aplysia*. In addition, long-lasting synaptic changes likely involve epigenetic changes in chromatin structure. During late LTP, phosphorylated CREB activates gene expression by recruiting the CREB binding protein (CBP), which acts as a histone acetylase, transferring an acetyl group to specific lysine residues on histone proteins, and thereby producing