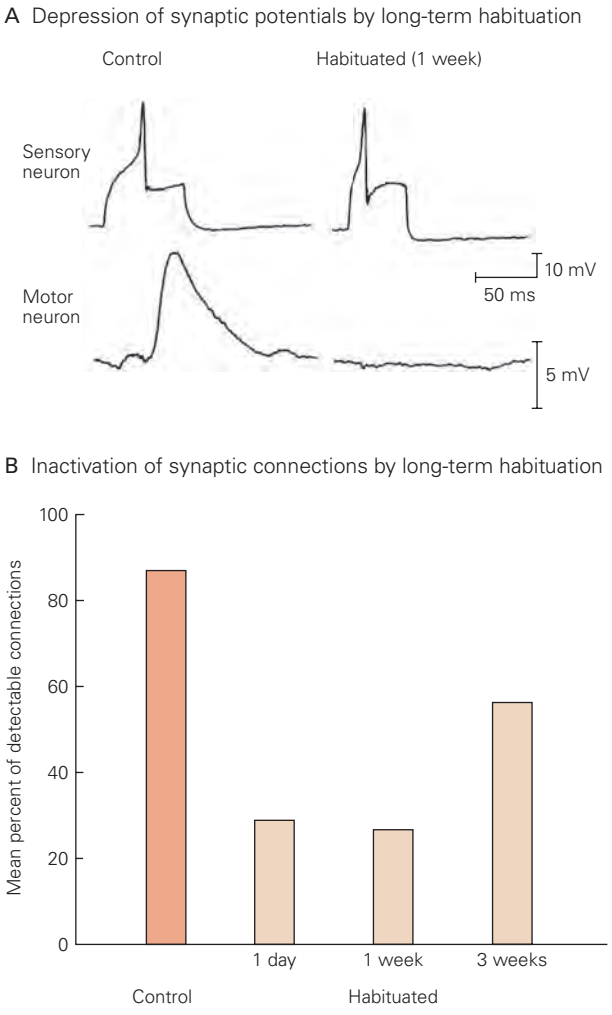


Figure 53–3 Long-term habituation of the gill-withdrawal reflex in *Aplysia.* (Adapted, with permission, from Castellucci, Carew, and Kandel 1978.)

A. Comparison of action potentials in sensory neurons and the postsynaptic potential in motor neurons in an untrained animal (control) and one that has been subjected to long-term habituation. In the habituated animal 1 week after training, no synaptic potential occurs in the motor neuron in response to the sensory neuron action potential.

B. After long-term habituation training, the mean percentage of sensory neurons making physiologically detectable connections with motor neurons is reduced even at 3 weeks.

Sensitization Involves Presynaptic Facilitation of Synaptic Transmission

The ability to recognize and respond to danger is necessary for survival. Not only snails and flies, but all animals, including humans, must distinguish predators from prey and hostile environments from safe ones. Because the ability to respond to threats is a universal requirement of survival, it has been conserved throughout evolution, allowing studies of invertebrates to shed light on neural mechanisms in mammals.

At the beginning of the 20th century, both Freud and Pavlov appreciated that anticipatory defensive responses to danger signals are biologically adaptive, a fact that likely accounts for the profound conservation of this capacity throughout vertebrates and invertebrates. In the laboratory, threat (fear) conditioning is typically studied by presenting a neutral stimulus, such as a tone, prior to the onset of an aversive stimulus, such as electrical shock. The two stimuli become associated such that the tone leads to the elicitation of defensive behaviors that protect against the harmful consequences predicted by the tone. Freud called this "signal anxiety," which prepares the individual for fight or flight when there is even the suggestion of external danger.

When an animal repeatedly encounters a harmless stimulus, its responsiveness to the stimulus habituates, as seen above. In contrast, when the animal confronts a *harmful* stimulus, it typically learns to respond more vigorously to a subsequent presentation of the same stimulus. Presentation of a harmful stimulus can even cause an animal to mount a defensive response to a subsequent *harmless* stimulus. As a result, defensive reflexes for withdrawal and escape become heightened. This enhancement of reflex responses is called *sensitization.*

Like habituation, sensitization can be transient or long lasting. A single shock to the tail of an *Aplysia* produces short-term sensitization of the gill-withdrawal reflex that lasts minutes; five or more shocks to the tail produce sensitization lasting days to weeks. Tail shock is also sufficient to overcome the effects of habituation and enhance a habituated gill-withdrawal reflex, a process termed *dishabituation*.

Sensitization and dishabituation result from an enhancement in synaptic transmission at several connections in the neural circuit of the gill-withdrawal reflex, including the connections made by sensory neurons with motor neurons and interneurons—the same synapses depressed by habituation (Figure 53–4A). Typically, modifiable synapses can be regulated bidirectionally, participate in more than one type of learning, and store more than one type of memory. The bidirectional synaptic changes that underlie habituation and sensitization are the result of different cellular mechanisms. In *Aplysia*, the same synapses that are weakened by habituation through a homosynaptic process can be strengthened by sensitization through a *heterosynaptic* process that depends on modulatory

interneurons activated by the harmful stimulus to the tail.

At least three groups of modulatory interneurons are involved in sensitization. The best studied use serotonin as a transmitter (Figure 53–4B). The serotonergic interneurons form synapses on many regions of the sensory neurons, including axo-axonic synapses on the presynaptic terminals of the sensory cells. After a single tail shock, the serotonin released from the interneurons binds to a receptor in the sensory neurons that is coupled to a stimulatory G protein that increases the activity of adenylyl cyclase. This action produces the second messenger cyclic adenosine monophosphate (cAMP), which in turn activates the cAMP-dependent protein kinase (PKA) (Chapter 14). Serotonin also activates a second type of G-protein–coupled receptor that leads to the hydrolysis of phospholipids and the activation of protein kinase C (PKC).

The protein phosphorylation mediated by PKA and PKC enhances the release of transmitter from sensory neurons through at least two mechanisms (Figure 53–4B). In one action, PKA phosphorylates a K^+ channel, causing it to close. This broadens the action potential and thus enhances the duration of Ca^{2+} influx through voltage-gated Ca^{2+} channels, which in turn enhances transmitter release. In a second action, protein phosphorylation through PKC enhances the functioning of the release machinery directly. Presynaptic facilitation in response to release of serotonin by a tail shock lasts for a period of many minutes. Repeated noxious stimuli can strengthen synaptic activity for days (by a mechanism we consider below).

Classical Threat Conditioning Involves Facilitation of Synaptic Transmission

Classical conditioning is a more complex form of learning. Rather than learning about the properties of one stimulus, as in habituation and sensitization, the animal learns to associate one type of stimulus with another. As described in Chapter 52, an initial weak conditioned stimulus (eg, the ringing of a bell) becomes highly effective in producing a response when paired with a strong unconditioned stimulus (eg, presentation of food). In reflexes that can be enhanced by both classical conditioning and sensitization, such as the defensive withdrawal reflexes of *Aplysia*, classical conditioning results in greater and longer-lasting enhancement.

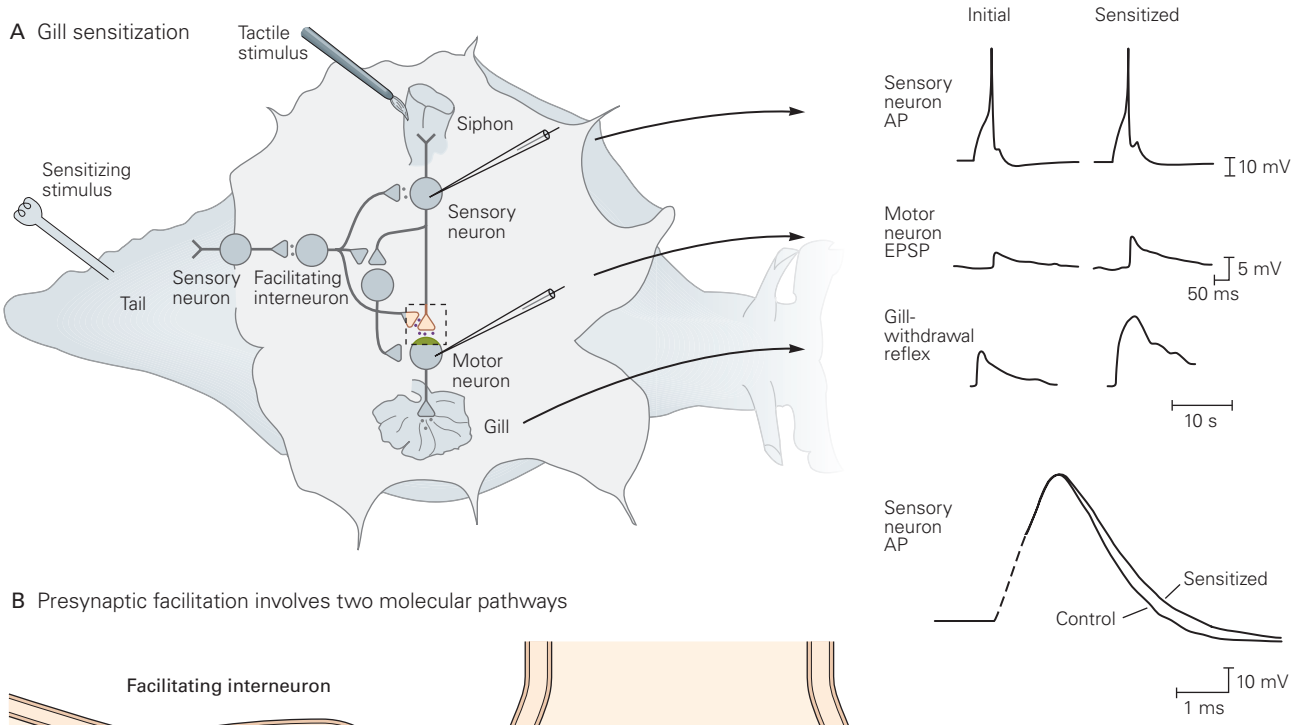
Although aversive classical conditioning is traditionally referred to as fear conditioning, we will use the more neutral term *threat conditioning* to avoid the implication that animals have subjective states comparable to those that humans experience and label as "fear." This distinction is important because humans can respond to threats behaviorally and physiologically in the absence of any reported feeling of fear. This terminology allows the findings from research on implicit learning in all animals, from the simplest worm to humans, to be interpreted in an objective manner without invoking empirically unverifiable subjective fear states in animals.

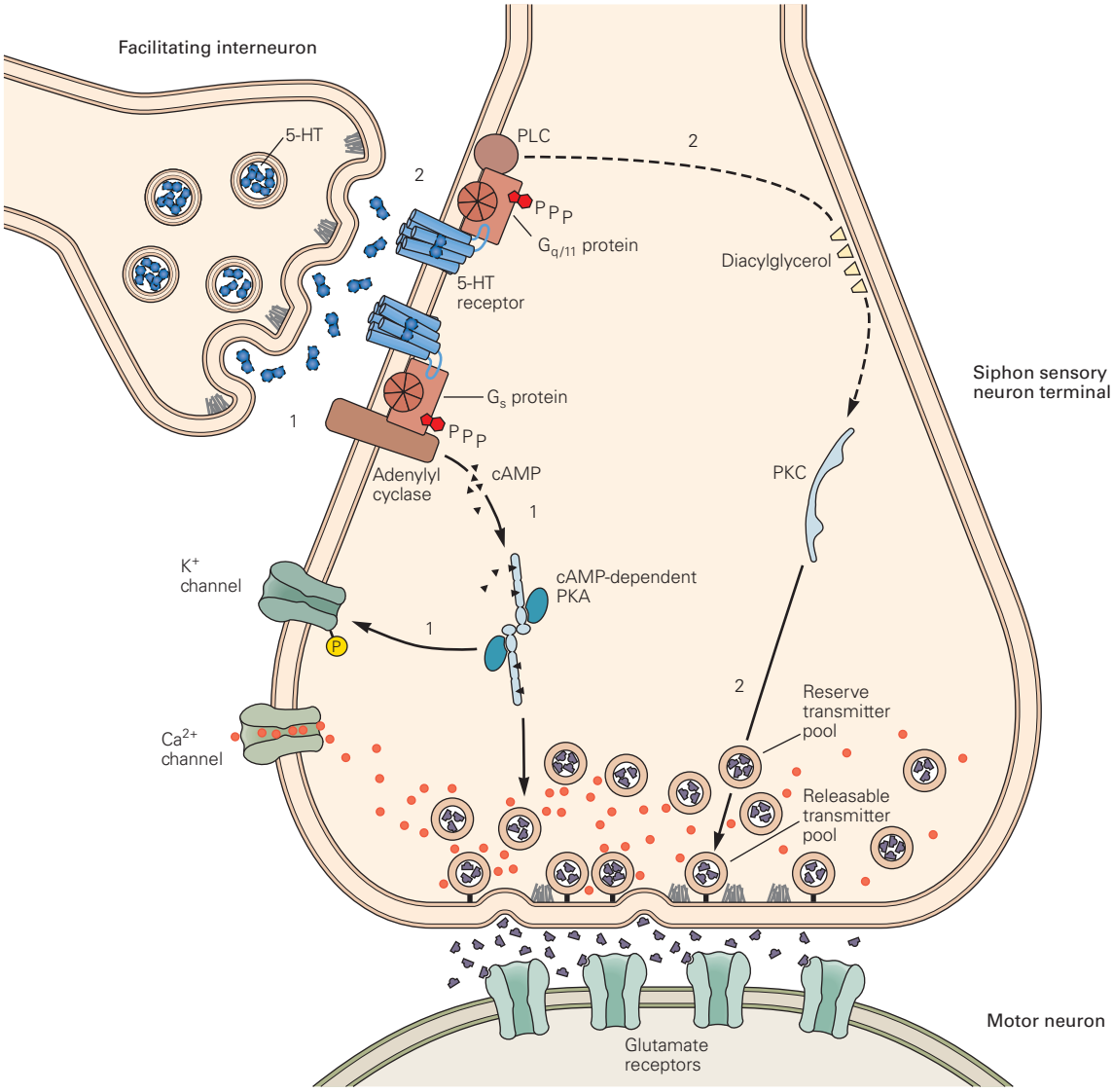
For classical conditioning of the *Aplysia* gill-withdrawal reflex, a weak touch to the siphon serves as the conditioned stimulus while a strong shock to the tail serves as the unconditioned stimulus. When the gill-withdrawal reflex is classically conditioned, gill withdrawal in response to siphon stimulation alone is greatly enhanced. This enhancement is even more dramatic than the enhancement produced in an unpaired pathway by tail shock alone (sensitization). In classical conditioning, the timing of the conditioned and unconditioned stimuli is critical. To be effective, the conditioned stimulus (siphon touch) must *precede* (and thus predict) the unconditioned stimulus (tail shock), often within an interval of about 0.5 seconds.

The convergence in individual sensory neurons of the signals initiated by the conditioned and unconditioned stimuli is critical. Alone, a strong shock to the tail (unconditioned stimulus) will excite serotonergic interneurons that form synapses on presynaptic terminals of the siphon sensory neurons, resulting in presynaptic facilitation (Figure 53–5A). However, when the tail shock immediately follows a slight tap on the siphon (conditioned stimulus), the serotonin from the interneurons produces even greater presynaptic facilitation, a process termed *activity-dependent facilitation* (Figure 53–5B).

How does this work? During conditioning, the modulatory interneurons activated by tail shock release serotonin shortly *after* the action potential produced in the siphon sensory neurons by the tap on the siphon. The action potential triggers an influx of Ca^{2+} into the presynaptic terminals of the sensory neurons, and the Ca^{2+} binds to calmodulin, which in turn binds to the enzyme, adenylyl cyclase. This primes the adenylyl cyclase so that it responds more vigorously to the serotonin released following the tail shock. This in turn enhances the production of cAMP, which increases the amount of presynaptic facilitation. If the order of stimuli is reversed so that serotonin release precedes Ca^{2+} influx in the presynaptic sensory terminals, there is no potentiation and no classical conditioning.

Thus, the cellular mechanism of classical conditioning in the monosynaptic pathway of the withdrawal reflex is largely an elaboration of the mechanism of


A Gill sensitization
Tactile stimulus
Siphon
Sensitizing stimulus
Sensory neuron
Facilitating interneuron
Tail
Sensory neuron
Motor neuron
Gill
Initial
Sensitized
Sensory neuron AP
10 mV
Motor neuron EPSP
5 mV
50 ms
Gill-withdrawal reflex
10 s
Sensory neuron AP
Sensitized
Control
10 mV
1 ms


B Presynaptic facilitation involves two molecular pathways
Facilitating interneuron
5-HT
PLC
2
P P P
$G_{q/11}$ protein
Diacylglycerol
5-HT receptor
G_s protein
Siphon sensory neuron terminal
P P P
Adenylyl cyclase
cAMP
PKC
1
K^+ channel
cAMP-dependent PKA
P
Reserve transmitter pool
Ca^{2+} channel
Releasable transmitter pool
Motor neuron
Glutamate receptors

sensitization, with the added feature that the adenylyl cyclase serves as a *coincidence detector* in the presynaptic sensory neuron, recognizing the temporal order of the physiological responses to the tail shock (unconditioned stimulus) and the siphon tap (conditioned stimulus).

In addition to the presynaptic component of activity-dependent facilitation, a postsynaptic component is triggered by Ca^{2+} influx into the motor neuron when it is highly excited by the siphon sensory neurons. The properties of this postsynaptic mechanism are similar to those of long-term potentiation of synaptic transmission in the mammalian brain (discussed later in this chapter and in Chapters 13 and 54).

Long-Term Storage of Implicit Memory Involves Synaptic Changes Mediated by the cAMP-PKA-CREB Pathway

Cyclic AMP Signaling Has a Role in Long-Term Sensitization

In all forms of learning, practice makes perfect. Repeated experience converts short-term memory into a long-term form. In *Aplysia*, the form of long-term memory that has been most intensively studied is long-term sensitization. Like the short-term form, long-term sensitization of the gill-withdrawal reflex involves changes in the strength of connections at several synapses. But in addition, it also recruits the growth of new synaptic connections.

Five spaced training sessions (or repeated applications of serotonin) over approximately 1 hour produce long-term sensitization and long-term synaptic facilitation lasting 1 or more days. Spaced training over several days produces sensitization that persists for 1 or more weeks. Long-term sensitization, like the short-term form, requires protein phosphorylation that is dependent on increased levels of cAMP (Figure 53–6).

The conversion of short-term memory into long-term memory, called *consolidation*, requires synthesis of messenger RNAs and proteins in the neurons in the circuit. Thus, activation of specific gene expression is required for long-term memory. The transition from short-term to long-term memory depends on the prolonged rise in cAMP that follows repeated applications of serotonin. The increase in cAMP leads to prolonged activation of PKA, allowing the catalytic subunit of the kinase to translocate into the nucleus of the sensory neurons. It also leads indirectly to activation of a second protein kinase, the mitogen-activated protein kinase (MAPK), a kinase commonly associated with cellular growth (Chapter 14). Within the nucleus, the catalytic subunit of PKA phosphorylates and thereby activates the transcription factor CREB-1 (*c*AMP *r*esponse *e*lement *b*inding protein 1), which binds a promoter element called CRE (*c*AMP *r*ecognition *e*lement) (Figures 53–6 and 53–7).

To turn on gene transcription, phosphorylated CREB-1 recruits a transcriptional coactivator, CREB-binding protein (CBP), to the promoter region. CBP has two important properties that facilitate transcriptional activation: It recruits RNA polymerase II to the

Figure 53–4 (Opposite) Short-term sensitization of the gill-withdrawal reflex in *Aplysia*.

A. Sensitization of the gill-withdrawal reflex is produced by applying a noxious stimulus to another part of the body, such as the tail. A shock to the tail activates tail sensory neurons that excite facilitating (modulatory) interneurons, which form synapses on the cell body and terminals of the mechanoreceptor sensory neurons that innervate the siphon. Through these axo-axonic synapses, the modulatory interneurons enhance transmitter release from the siphon sensory neurons onto their postsynaptic gill motor neurons (presynaptic facilitation), thus enhancing gill withdrawal. Presynaptic facilitation results, in part, from a prolongation of the sensory neuron action potential (**AP**; **bottom traces**). (Abbreviation: **EPSP**, excitatory postsynaptic potential.) (Adapted, with permission, from Pinsker et al. 1970; Klein and Kandel 1980.)

B. Presynaptic facilitation in the sensory neuron is thought to occur by means of two biochemical pathways. The diagram shows details of the synaptic complex in the dashed box in part **A**.

Pathway 1: A facilitating interneuron releases serotonin (**5-HT**), which binds to metabotropic receptors in the sensory neuron terminal. This action engages a G protein (G_s), which in turn increases the activity of adenylyl cyclase. The adenylyl cyclase converts adenosine triphosphate to cyclic adenosine monophosphate (**cAMP**), which binds to the regulatory subunit of protein kinase A (**PKA**), thus activating its catalytic subunit. The catalytic subunit phosphorylates certain K^+ channels, thereby closing the channels and decreasing the outward K^+ current. This prolongs the action potential, thus increasing the influx of Ca^{2+} through voltage-gated Ca^{2+} channels and thereby augmenting transmitter release.

Pathway 2: Serotonin binds to a second class of metabotropic receptor that activates the $G_{q/11}$ class of G protein that enhances the activity of phospholipase C (**PLC**). The PLC activity leads to production of diacylglycerol, which activates protein kinase C (**PKC**). The PKC phosphorylates presynaptic proteins, resulting in the mobilization of vesicles containing glutamate from a reserve pool to a releasable pool at the active zone, thus increasing the efficiency of transmitter release.

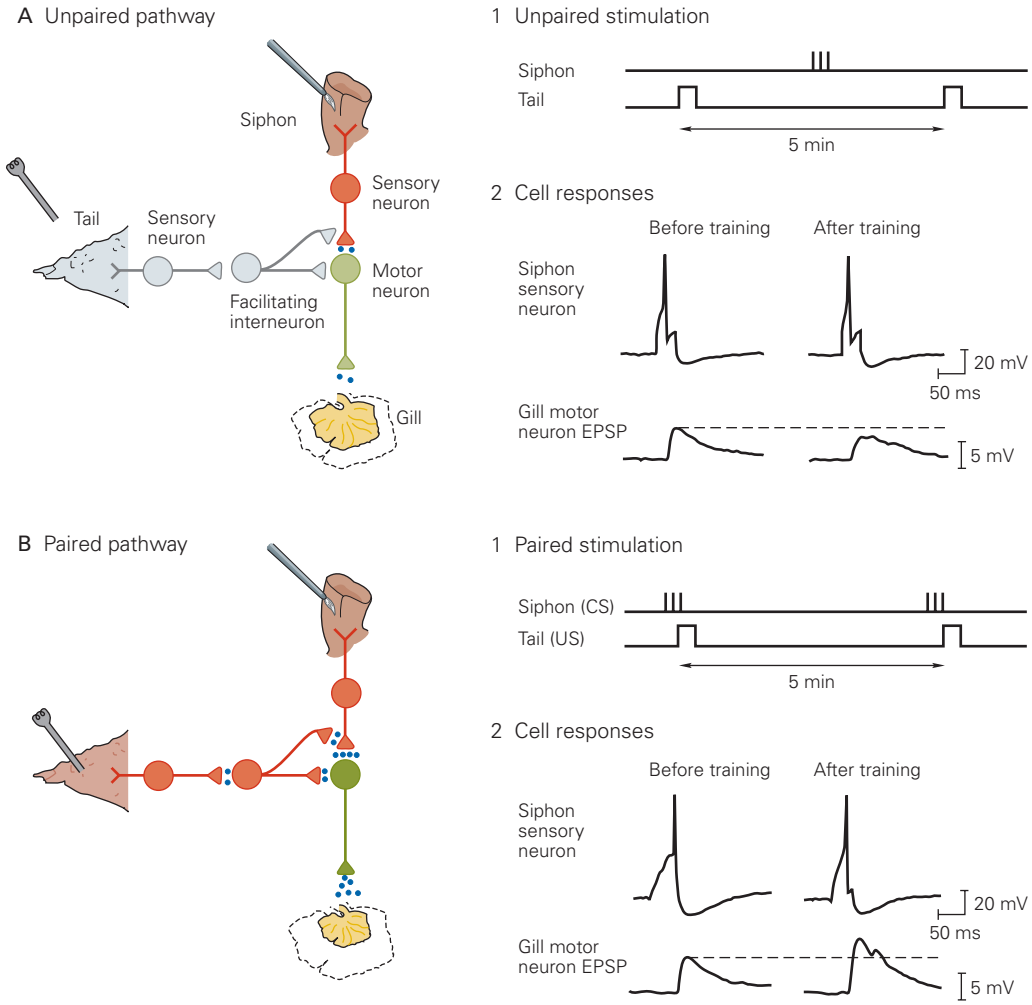


Figure 53–5 Classical conditioning of the gill-withdrawal reflex in *Aplysia*. (Adapted, with permission, from Hawkins et al. 1983.)

A. The siphon is stimulated by a light tap and the tail is shocked, but the two stimuli are not paired in time. The tail shock excites facilitatory interneurons that form synapses on the presynaptic terminals of sensory neurons innervating the mantle shelf and siphon. This is the mechanism of sensitization. **1.** The pattern of unpaired stimulation during training. **2.** Under these conditions, the size of the motor neuron test excitatory postsynaptic potential (**EPSP**) is only weakly facilitated by the tail shock. Often, as in this example, the EPSP actually decreases slightly despite the tail shock because repeated unpaired stimulation of the siphon leads to synaptic depression due to habituation.

B. The tail shock is paired in time with stimulation of the siphon. **1.** The siphon is touched (conditioned stimulus [**CS**]) immediately prior to shocking the tail (unconditioned stimulus [**US**]). As a result, the siphon sensory neurons are primed to be more responsive to input from the facilitatory interneurons in the unconditioned pathway. This is the mechanism of classical conditioning; it selectively amplifies the response of the conditioned pathway. **2.** Recordings of test EPSPs in an identified motor neuron produced by a siphon sensory neuron before training and 1 hour after training. After training with paired sensory input, the EPSP in the siphon motor neuron is considerably greater than either the EPSP before training or the EPSP following unpaired tail shock (shown in part **A2**). This synaptic amplification produces a more vigorous gill withdrawal.

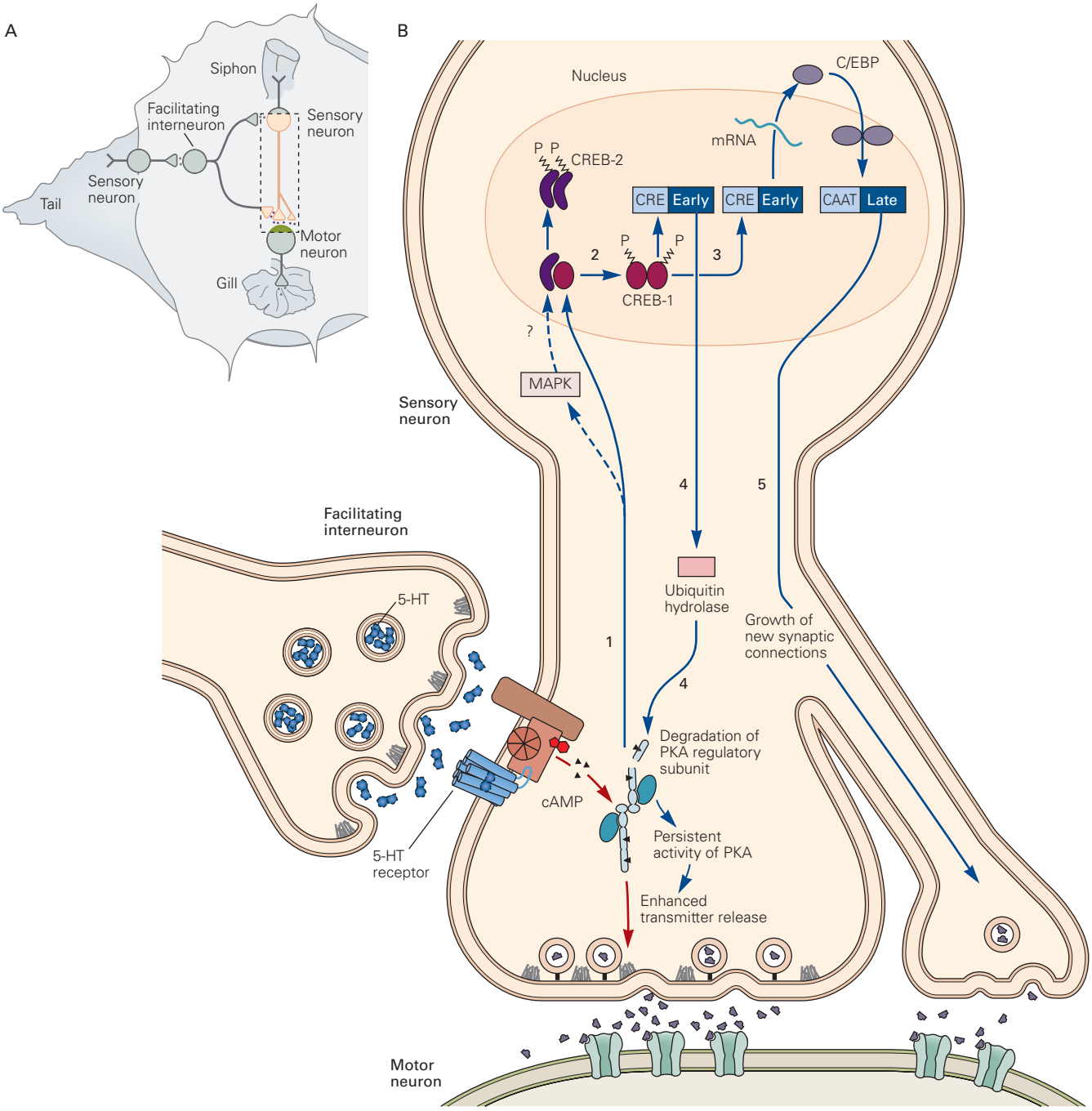
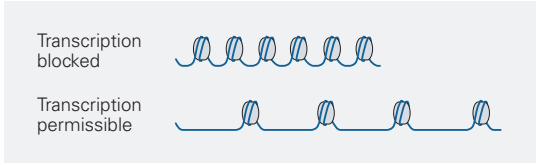


Figure 53–6 Long-term sensitization involves synaptic facilitation and the growth of new synaptic connections.

A. Long-term sensitization of the gill-withdrawal reflex of *Aplysia* involves long-lasting facilitation of transmitter release at the synapses between sensory and motor neurons.

B. Long-term sensitization of the gill-withdrawal reflex leads to persistent activity of protein kinase A (**PKA**), resulting in the growth of new synaptic connections. Repeated tail shock leads to more pronounced elevation of cyclic adenosine monophosphate (**cAMP**), producing long-term facilitation (lasting 1 or more days) that outlasts the increase in cAMP and recruits the synthesis of new proteins. This inductive mechanism is initiated by translocation of PKA to the nucleus (**pathway 1**), where PKA phosphorylates the transcriptional activator cAMP response element binding protein 1 (**CREB-1**) (**pathway 2**). CREB-1 binds cAMP regulatory elements (**CRE**) located in the upstream region of several cAMP-inducible genes, activating gene transcription (**pathway 3**). PKA also activates the mitogen-activated protein kinase (**MAPK**), which phosphorylates the transcriptional repressor cAMP response element binding protein 2 (**CREB-2**), thus removing its repressive action. One gene activated by CREB-1 encodes a ubiquitin hydrolase, a component of a specific ubiquitin proteasome that leads to the proteolytic cleavage of the regulatory subunit of PKA, resulting in persistent activity of PKA, even after cAMP has returned to its resting level (**pathway 4**). CREB-1 also activates the expression of the transcription factor C/EBP, which leads to expression of a set of unidentified proteins important for the growth of new synaptic connections (**pathway 5**).



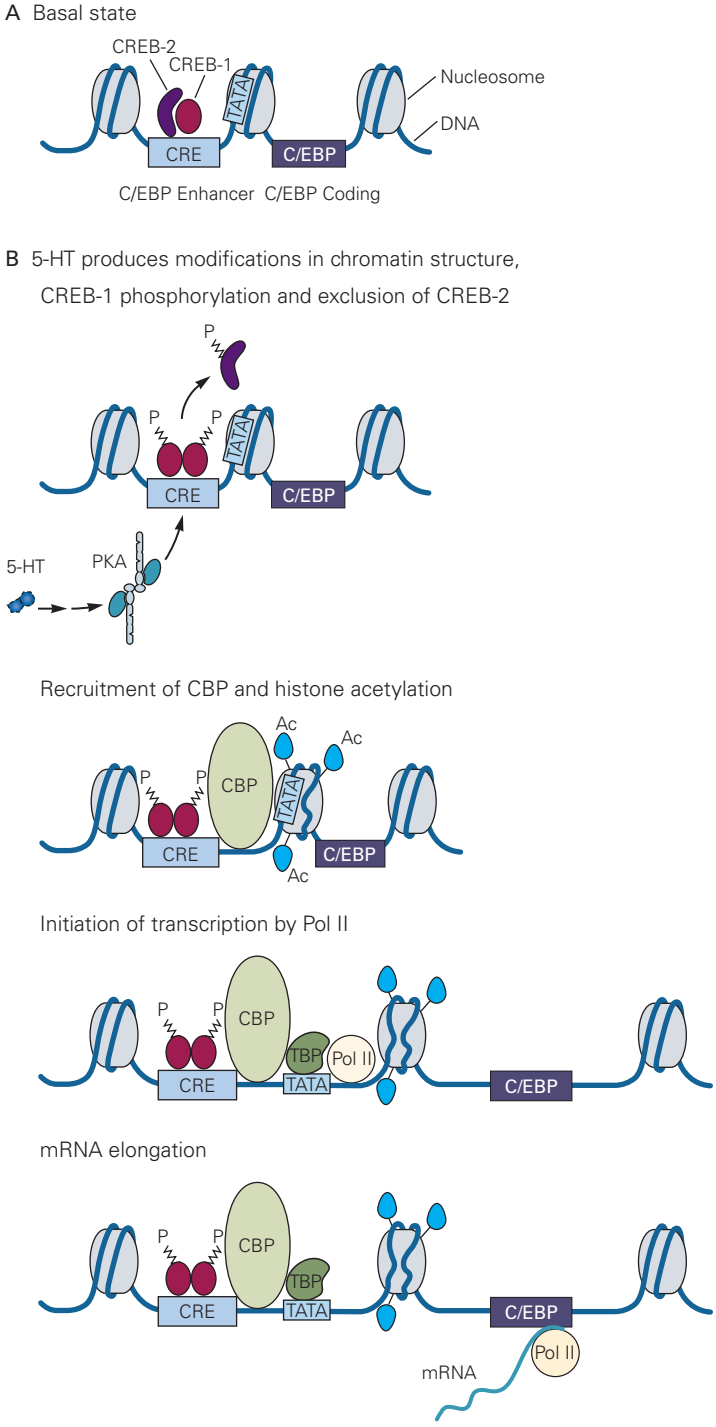


Figure 53–7 Regulation of histone acetylation by serotonin, CREB-1, and CBP.

A. Under basal conditions, the activator CREB-1 (here in complex with CREB-2) occupies the binding site for cAMP recognition element (**CRE**) within the promoter region of its target genes. In the example shown here, CREB-1 binds to the CRE within the C/EBP promoter. In the basal state, CREB-1 binding is not able to activate transcription because the TATA box, the core promoter region responsible for recruiting RNA polymerase II (**Pol II**) during transcription initiation, is inaccessible because the DNA is tightly bound to histone proteins in the nucleosome.

B. Serotonin (**5-HT**) activates protein kinase A (**PKA**), which phosphorylates CREB-1 and indirectly enhances CREB-2 phosphorylation by MAPK, causing CREB-2 to dissociate from the promoter. This allows CREB-1 to form a complex at the promoter with CREB binding protein (**CBP**). Activated CBP acetylates specific lysine residues of the histones, causing them to bind less tightly to DNA. Along with other changes in chromatin structure, acetylation facilitates the repositioning of the nucleosome that previously blocked access of the Pol II complex to the TATA box. This repositioning allows Pol II to be recruited to initiate transcription of the C/EBP gene. (Abbreviation: **TBP**, TATA binding protein.)

promoter, and it functions as an acetyltransferase, adding acetyl groups to certain lysine residues on its substrate proteins. One of the most important substrates of CBP are DNA-binding histone proteins, which are components of nucleosomes, the fundamental building blocks of chromatin. The histones contain a series of positively charged basic residues that strongly interact with the negatively charged phosphates of DNA. This interaction causes DNA to become tightly wrapped around the nucleosomes, much like string is wrapped around a spool, thereby preventing necessary transcription factors from accessing their gene targets.

The binding of CBP to CREB-1 leads to histone acetylation, which causes a number of important structural and functional changes at the level of the nucleosome. For example, acetylation neutralizes the positive charge of lysine residues in the histone tail domains, decreasing the affinity of histones for DNA. Also, specific classes of transcriptional activators can bind to acetylated histones and facilitate the repositioning of nucleosomes at the promoter region. Together, these and other types of chromatin modifications serve to regulate the accessibility of chromatin to the transcriptional machinery, and thus enhance the ability of a gene to be transcribed. This type of modification of DNA structure is termed *epigenetic* regulation. As we will see in Chapter 54, a mutation in the gene encoding CBP underlies Rubinstein-Taybi syndrome, a disorder associated with mental retardation.

The turning on of transcription by PKA also depends on its ability to indirectly activate the MAPK pathway (Chapter 14). MAPK phosphorylates the transcription factor CREB-2, relieving its inhibitory action on transcription (Figure 53–6B). The combined effects of CREB-1 activation and relief of CREB-2 repression induce a cascade of new gene expression important for learning and memory (Figure 53–7).

The presence of both a repressor (CREB-2) and an activator (CREB-1) of transcription at the first step in long-term facilitation suggests that the threshold for long-term memory storage can be regulated. Indeed, we see in everyday life that the ease with which short-term memory is transferred into long-term memory varies greatly with attention, mood, and social context.

The Role of Noncoding RNAs in the Regulation of Transcription

There are other targets of transcription and chromatin regulation in memory consolidation and reconsolidation besides messenger RNAs. Of particular interest are noncoding RNAs such as microRNAs (miRNAs), PIWI-interacting RNAs (piRNAs), and long noncoding RNAs. These are also targeted to specific genetic sites, and their expression in turn regulates transcriptional and posttranscriptional mechanisms.

Studies in *Aplysia* show that miRNAs and piRNAs are both regulated by neuronal activity and contribute to long-term facilitation. MicroRNAs are a class of conserved noncoding RNAs, 20 to 23 nucleotides in length, that contribute to transcriptional and posttranscriptional regulation of gene expression through a specific set of RNA–protein machinery. In *Aplysia*, the most abundant and conserved brain species of these miRNAs are present in sensory neurons, where one of them—miRNA-124—normally constrains serotonin-induced synaptic facilitation by inhibiting the translation of CREB-1 mRNA, suppressing levels of CREB-1 protein. Serotonin inhibits the synthesis of miRNA-124, thereby leading to the disinhibition of the translation of CREB-1 mRNA, enabling the initiation of CREB-1–mediated transcription. The piRNAs are 28 to 32 nucleotides in length, slightly longer than miRNAs, and bind to a protein called Piwi. Individual piRNAs promote the methylation of specific DNA sequences, thereby silencing the genes, providing another example of epigenetic regulation. One piRNA, piRNA-F, increases in response to serotonin, which leads to the methylation of the promoter of CREB-2, reducing CREB-2 gene transcription.

Thus, we see here an example of integrative action at the transcriptional level. Serotonin regulates both piRNA and microRNA in a coordinated fashion: Serotonin rapidly decreases levels of miRNA-124 and facilitates the activation of CREB-1, which begins the process of memory consolidation. After a delay, serotonin also increases levels of piRNA-F, resulting in the methylation and silencing of the promoter of the transcription repressor CREB-2. The decrease in CREB-2 increases the duration of action of CREB-1, thereby consolidating a stable form of long-term memory in the sensory neuron (Figure 53–8).

Two of the genes expressed in the wake of CREB-1 activation and the consequential alteration in chromatin structure are important in the early development of long-term facilitation. One is a gene for ubiquitin carboxyterminal hydrolase, the other a gene for a transcription factor, CAAT box enhancer binding protein (C/EBP), a component of a gene cascade necessary for synthesizing proteins needed for the growth of new synaptic connections (Figures 53–6 and 53–7).

The hydrolase facilitates ubiquitin-mediated protein degradation (Chapter 7) and helps enhance activation of PKA. PKA is made up of four subunits; two regulatory subunits inhibit two catalytic subunits (Chapter 14). With long-term training and the

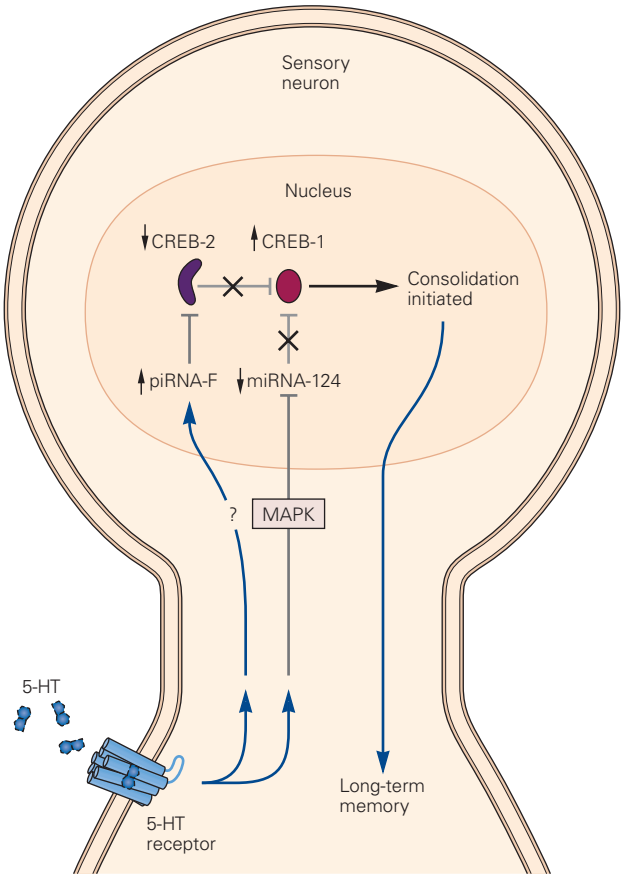


Figure 53–8 Small non-coding RNA molecules contribute to the memory consolidation switch. Long-term facilitation of the sensory to motor neuron synapses is consolidated through the action of two distinct classes of small noncoding RNA molecules. miRNA-124 normally acts to suppress levels of the CREB-1 transcription factor by binding to its mRNA and inhibiting its translation. Serotonin (**5-HT**) downregulates miRNA-124 levels through a mechanism requiring mitogen-activated protein kinase (**MAPK**). This enhances the levels of CREB-1, promoting activation of CREB-1–dependent transcription of gene products necessary for memory consolidation. In a complementary pathway, 5-HT enhances with a delay the synthesis of several piRNAs, including piRNA-F, which bind to the Piwi protein. The piRNA-F/Piwi complex leads to enhanced methylation of the *CREB-2* gene, resulting in long-lasting transcriptional repression of *CREB-2* and decreased levels of CREB-2 protein. Because CREB-2 normally inhibits the action of CREB-1, the increased levels of piRNA-F in response to 5-HT enhance and prolong CREB-1 activity, resulting in more effective memory consolidation.

induction of the hydrolase, approximately 25% of the regulatory subunits are degraded in the sensory neurons. As a result, free catalytic subunits can continue to phosphorylate proteins important for the enhancement of transmitter release and the strengthening of synaptic connections, including CREB-1, long after cAMP has returned to its resting level (Figure 53–6B). Formation of a constitutively active enzyme is therefore the simplest molecular mechanism for long-term memory. With repeated training, a second-messenger kinase critical for short-term facilitation can remain persistently active for up to 24 hours without requiring a continuous activating signal.

The second and more enduring consequence of CREB-1 activation is the activation of the transcription factor C/EBP. This transcription factor forms both a homodimer with itself and a heterodimer with another transcription factor called *activating factor*. Together, these factors act on downstream genes that trigger the growth of new synaptic connections that support long-term memory.

With long-term sensitization, the number of presynaptic terminals in the sensory neurons in the gill-withdrawal circuit doubles (Figure 53–9). The dendrites of the motor neurons also grow to accommodate the additional synaptic input. Thus, long-term structural changes in both post- and presynaptic cells increase the number of synapses. Long-term habituation, in contrast, leads to *pruning* of synaptic connections, as described above. Long-term disuse of functional connections between sensory and motor neurons reduces the number of terminals of each sensory neuron by one-third (Figure 53–9A).

Long-Term Synaptic Facilitation Is Synapse Specific

A typical pyramidal neuron in the mammalian brain makes 10,000 presynaptic connections with a wide range of target cells. It is therefore generally thought that long-term memory storage should be synapse specific—that is, only those synapses that actively participate in learning should be enhanced. However, the finding that long-term facilitation involves gene expression—which occurs in the nucleus, far removed from a neuron's synapses—raises some fundamental questions regarding information storage.

Is long-term memory storage indeed synapse specific, or do the gene products recruited during long-term memory storage alter the strength of every presynaptic terminal in a neuron? And if long-term memory is synapse specific, what are the cellular mechanisms that enable the products of gene transcription to selectively strengthen just some synapses and not others?

Kelsey Martin and her colleagues addressed these questions for long-term facilitation by using a cell culture system consisting of an isolated *Aplysia* sensory neuron with a bifurcated axon that makes separate synaptic contacts with two motor neurons. The sensory