Neuroscience - Problem Drill 22: Learning and Memory Mechanisms

Question No. 1 of 10

Instructions: (1) Read the problem and answer choices carefully, (2) Work the problems on paper as needed, (3) Pick the answer, and (4) Review the core concept tutorial as needed.

Question #01

1. Which of the following is FALSE regarding how information is stored?

   (A) Experience-dependent changes reflect synaptic modifications and these store information.
   (B) Information is located in small, specific areas of the brain.
   (C) Memories are encoded as specific patterns of synaptic change.
   (D) Learning is the acquisition of new information or knowledge.
   (E) Memory is the retention of new information.

Feedback on Each Answer Choice

A. Incorrect!
   It is true that experience-dependent changes reflect synaptic modifications and these store information

B. Correct!
   Information is widely distributed in the brain.

C. Incorrect!
   It is true that memories are encoded as specific patterns of synaptic change

D. Incorrect!
   It is true that learning is the acquisition of new information or knowledge

E. Incorrect!
   It is true that memory is the retention of new information.

Solution

In our exploration of the neurobiology of memory, this tutorial will address the important question regarding how information is stored. Neural network models suggest that the experience-dependent changes in selectivity of individual neurons reflect synaptic modifications that, distributed over many neurons, store information. From this perspective, memories are encoded as specific patterns of synaptic change, with some synapses growing stronger and others growing weaker. We do know that memories can result from subtle alterations in synapses and these alterations can be widely distributed in the brain. This helps narrow down the search for a physical basis of memory but also leads to a difficulty. The synaptic modifications that underlie memory may be too small and too widely distributed to be observed and studied experimentally. This has lead to the use of simple invertebrate animals for insights about the molecular mechanisms of memory. This is especially applicable for procedural memory and the study of synaptic plasticity. With this basis of knowledge, research can then branch into the study of mammalian brains using electrical stimulation with some interesting findings. We will cover all of these topics in this tutorial as well as a more focused look at particular structures involved. It is also important to be very clear as to the difference between learning and memory. Learning is the acquisition of new information or knowledge. Memory is the retention of learned information.

The correct answer is (B).
## Question No. 2 of 10

**Instructions:** (1) Read the problem and answer choices carefully, (2) Work the problems on paper as needed, (3) Pick the answer, and (4) Review the core concept tutorial as needed.

<table>
<thead>
<tr>
<th>Question #02</th>
<th>1. Which of the following statements is TRUE regarding nonassociative learning?</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>(A) Sensitization is learning to ignore a stimulus that lacks meaning.</td>
</tr>
<tr>
<td></td>
<td>(B) Procedural memories are not robust and form along complex pathways.</td>
</tr>
<tr>
<td></td>
<td>(C) Habituation involves learning to intensify your response to all stimuli.</td>
</tr>
<tr>
<td></td>
<td>(D) Classical conditioning is a type of nonassociative learning.</td>
</tr>
<tr>
<td></td>
<td>(E) Nonassociative learning describes the change in behavioral response that occurs over time in response to a single type of stimulus.</td>
</tr>
</tbody>
</table>

| Feedback on Each Answer Choice | A. Incorrect!  
Sensitization involves learning to intensify your response to all stimuli, even ones that previously evoked little or no reaction. |
|-------------------------------|----------------------------------------------------------------------------------------------------------------------------------|
|                               | B. Incorrect!  
Procedural or nondeclarative memories are particularly robust and can be formed along simple reflex pathways that link sensation to movements. |
|                               | C. Incorrect!  
Habituation is learning to ignore a stimulus that lacks meaning. |
|                               | D. Incorrect!  
The two types of nonassociative learning are habituation and sensitization. |
|                               | E. Correct!  
It is true that nonassociative learning describes the change in behavioral response that occurs over time in response to a single type of stimulus. |

| Solution | Let’s focus on procedural memory, or memory of skills, habits, and behaviors. We learn to play a musical instrument, throw a Frisbee, or tie our shoes and somewhere, that information is stored in our brain. Generally, nondeclarative memories cannot be accessed for conscious recollection. As the old saying goes, you never forget how to ride a bicycle. Recall that procedural learning involves learning a motor response (procedure) in reaction to a sensory input. These memories are particularly robust and can be formed along simple reflex pathways that link sensation to movements. Procedural memory is typically broken down into two categories: nonassociative learning and associative learning. Let’s look at each of these in more detail.  
Nonassociative learning describes the change in behavioral response that occurs over time in response to a single type of stimulus. There are two types: habituation and sensitization.  
Habituation is learning to ignore a stimulus that lacks meaning. You are habituated to a lot of stimuli. Perhaps as you read this sentence, cars and trucks are passing outside, a dog is barking, your roommate is playing U2 for the hundredth time; and all this goes on without you really noticing. You have been habituated to these stimuli.  
Sensitization involves learning to intensify your response to all stimuli, even ones that previously evoked little or no reaction. Suppose you are walking down a familiar sidewalk on a well-lit city street at night and suddenly there is a blackout. You hear footsteps behind you and though normally this wouldn’t disturb you, now you almost jump out of your skin. Car headlights appear and you react by sidestepping away from the street. The strong sensory stimulus caused sensitization.  

The correct answer is (E). |
**Question No. 3 of 10**

**Instructions:** (1) Read the problem and answer choices carefully, (2) Work the problems on paper as needed, (3) Pick the answer, and (4) Review the core concept tutorial as needed.

### Question #03

3. Which of the following statements is TRUE regarding Associative learning?

- **(A)** Classical and instrumental conditionings are types of nonassociative learning.
- **(B)** Instrumental conditioning involves associating stimulus that evokes a measurable response with a second stimulus that normally does not evoke this response.
- **(C)** Timing is critical in successful classical conditioning.
- **(D)** In classical conditioning, an individual learns to associate a response, such as a motor act, with a meaningful stimulus; a reward such as food.
- **(E)** Instrumental conditioning only works with a reward that is food or drink.

### Feedback on Each Answer Choice

<table>
<thead>
<tr>
<th>Choice</th>
<th>Feedback</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Incorrect!</td>
<td>Both classical and instrumental conditionings are types of associative learning because they involve forming associations between events.</td>
</tr>
<tr>
<td>B. Incorrect!</td>
<td>It is classical conditioning that involves associating stimulus that evokes a measurable response (unconditional stimulus) with a second stimulus that normally does not evoke this response (conditional stimulus).</td>
</tr>
<tr>
<td>C. Correct!</td>
<td>It is true that timing is critical in successful classical conditioning.</td>
</tr>
<tr>
<td>D. Incorrect!</td>
<td>It is in instrumental conditioning that an individual learns to associate a response, such as a motor act, with a meaningful stimulus; a reward such as food.</td>
</tr>
<tr>
<td>E. Incorrect!</td>
<td>Many experiments have shown that rats will also lever-press for a cocaine reward or for electrical stimulation of the medial forebrain bundle.</td>
</tr>
</tbody>
</table>

### Solution

During associative learning, we form associations between events. Two types are usually distinguished: classical conditioning and instrumental conditioning.

Classical conditioning involves associating stimulus that evokes a measurable response (unconditional stimulus) with a second stimulus that normally does not evoke this response (conditional stimulus).

Timing is critical in successful classical conditioning. Conditioning will occur if the unconditional stimulus and the conditional stimulus are presented simultaneously, or if the conditional stimulus precedes the unconditional stimulus by a short interval. However, if the conditional stimulus precedes the unconditional stimulus by too much, the conditioning will be much weaker or absent. Conditioning typically does not occur if the conditional stimulus follows the unconditional stimulus.

In instrumental conditioning, an individual learns to associate a response, such as a motor act, with a meaningful stimulus; a reward such as food. For example, rats can be easily trained to press a lever they discover in their cage if doing so will produce a food reward. At first, it is by chance that they first press the lever but after a few happy accidents, the rat soon learns to continually press the lever until it is no longer hungry. The same can be shown in primates. However the reward need not be just food or drink. Many experiments have shown that rats will lever-press for a cocaine reward or for electrical stimulation of the medial forebrain bundle. It is interesting to note that instrumental conditioning will also occur if a response, instead of evoking a rewarding stimulus, prevents the occurrence of an aversive stimulus, such as a foot shock.

**The correct answer is (C).**
### Instructions:
(1) Read the problem and answer choices carefully, (2) Work the problems on paper as needed, (3) Pick the answer, and (4) Review the core concept tutorial as needed.

<table>
<thead>
<tr>
<th>Question #04</th>
</tr>
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<tbody>
<tr>
<td>4. All of the following is TRUE regarding studies of involving Aplysia (sea slug)?</td>
</tr>
<tr>
<td>(A) The reflex used in studies of Aplysia is the eye blink reflex.</td>
</tr>
<tr>
<td>(B) Repeated presentations of a water jet to Aplysia’s siphon will result in sensitization.</td>
</tr>
<tr>
<td>(C) Repeated stimulation of the siphon skin leads to progressively less contraction of the gill-withdrawal muscles due to weakening of the muscle.</td>
</tr>
<tr>
<td>(D) Habituation takes place at the synapse between the sensory and motor neuron.</td>
</tr>
<tr>
<td>(E) The sensory neuron fired action potentials less and less in response to skin stimulation, even as the motor response decreased.</td>
</tr>
</tbody>
</table>

<table>
<thead>
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<th>Feedback on Each Answer Choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Incorrect! In Aplysia, if a jet of water is squirted onto its fleshy region, referred to as its siphon, its gill will retract in what is called the gill-withdrawal reflex.</td>
</tr>
<tr>
<td>B. Incorrect! In Aplysia, the gill-withdrawal reflex displays habituation after repeated presentations of the water jet unto the siphon.</td>
</tr>
<tr>
<td>C. Incorrect! Repeated stimulation of the siphon skin leads to progressively less contraction of the gill-withdrawal muscles but the muscle was ruled out as the location of habituation by electrically stimulating the motor neuron (L7) and showing that it always evoked the same amount of muscle contraction.</td>
</tr>
<tr>
<td>D. Correct! It is true habituation takes place at the synapse between the sensory and motor neuron.</td>
</tr>
<tr>
<td>E. Incorrect! The sensory neuron continued to fire action potentials in response to skin stimulation, even as the motor response decreased.</td>
</tr>
</tbody>
</table>
Nonassociative learning has been studied extensively in the sea slug Aplysia californica. If someone blows gently on your eye, you will blink, however, over time you will habituate (as long as the air puff isn’t painful). In Aplysia, if a jet of water is squirted onto its fleshy region, referred to as its siphon, its gill will retract in what is called the gill-withdrawal reflex. Like the eye blink, the gill-withdrawal reflex displays habituation after repeated presentations of the water jet. Beginning in the 1960’s, a pioneering series of experiments set out to determine where this procedural memory resides and how it is formed.

The first important question concerns where the habituation occurs. Repeated stimulation of the siphon skin leads to progressively less contraction of the gill-withdrawal muscles. The change underlying this habituation could occur at a number of points along the circuit such as: at the sensory nerve endings in the skin, making them less sensitive to the squirt of water; at the muscle, making it less responsive to synaptic stimulation by the motor neuron; or at the synapse between the sensory neuron and the motor neuron. The sensory nerve endings in the skin were ruled out using microelectrode recordings from the sensory neuron as habituation occurred. The sensory neuron continued to fire action potentials in response to skin stimulation, even as the motor response decreased. Similarly, the muscle was ruled out as the location of habituation by electrically stimulating the motor neuron (L7) and showing that it always evoked the same amount of muscle contraction. This leaves the third possibility: habituation takes place at the synapse between the sensory and motor neuron. This was shown to be true by repetitive electrical stimulation to the sensory neuron and showing this to be sufficient to cause a progressive decrease in the size of the postsynaptic EPSP.

The correct answer is (D).
Question No. 5 of 10

**Instructions:** (1) Read the problem and answer choices carefully, (2) Work the problems on paper as needed, (3) Pick the answer, and (4) Review the core concept tutorial as needed.

**Question #05**

5. Which of the following is NOT true regarding sensitization in Aplysia?

(A) the neurotransmitter released by L29 is serotonin.
(B) The release of serotonin sets in motion a cascade in the presynaptic terminal.
(C) The cascade initiated by the release of serotonin is a tyrosine kinase pathway.
(D) It is the cAMP that sensitizes the sensory terminal so that it lets in more calcium per action potential.
(E) Persistent sensitization is also associated with increased postsynaptic responses to the neurotransmitter released by the sensory nerve.

**Feedback on Each Answer Choice**

- **A. Incorrect!**
  It is true that the neurotransmitter released by L29 is serotonin.

- **B. Incorrect!**
  It is true that the release of serotonin sets in motion a cascade in the presynaptic terminal.

- **C. Correct!**
  The cascade initiated in this response is one that is well known in cell biology. It is the standard G-protein coupled receptor (GPCR) response.

- **D. Incorrect!**
  It is true that it is the cAMP that sensitizes the sensory terminal so that it lets in more calcium per action potential.

- **E. Incorrect!**
  It is true that persistent sensitization is also associated with increased postsynaptic responses to the neurotransmitter released by the sensory nerve.

**Solution**

When discussing sensitization in Aplysia, the neurotransmitter released by L29 is serotonin which sets in motion a cascade in the presynaptic terminal that sensitizes the sensory terminal so that it lets in more calcium per action potential. The more calcium that enters the presynaptic terminal, the more neurotransmitter that is released.

The cascade initiated in this response is one that is well known in cell biology. It is the standard G-protein coupled receptor (GPCR) response. The stimulation of GPCR leads to the activation of the enzyme adenyl cyclase to form intracellular second messengers. In the case of Aplysia, the second messenger formed is cyclic AMP (cAMP). It is the cAMP that sensitizes the sensory terminal so that it lets in more calcium per action potential.

Recent research suggests that the activation of L29 does not only affect the presynaptic neuron in the circuit. Persistent sensitization is also associated with increased postsynaptic responses to the neurotransmitter released by the sensory nerve. This neurotransmitter is glutamate and sensitization is partly explained by the delivery of new glutamate receptors to the synapse.

**The correct answer is (C).**
<table>
<thead>
<tr>
<th>Question #06</th>
<th>6. Which of the following is TRUE regarding the cerebellar cortex?</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Correct!</td>
<td>It is true that The cerebellar cortex consists of two layers of neuronal cell bodies, the Purkinje cell layer and the granule cell layer and these are separated from the pial surface by a molecular layer that is largely devoid of somata.</td>
</tr>
<tr>
<td>B. Incorrect!</td>
<td>Purkinje cell dendrites extend only into the molecular layer</td>
</tr>
<tr>
<td>C. Incorrect!</td>
<td>While it is true that Purkinje cell axons synapse on neurons in the deep cerebellar nuclei, these nuclei are the major output cells of the cerebellum.</td>
</tr>
<tr>
<td>D. Incorrect!</td>
<td>Purkinje cells use GABA as a neurotransmitter so their influence on cerebellular output is inhibitory.</td>
</tr>
<tr>
<td>E. Incorrect!</td>
<td>Climbing fibers are axons from the inferior olive while mossy fibers are axons from pontine nuclei.</td>
</tr>
</tbody>
</table>
**Solution**

The cerebellar cortex consists of two layers of neuronal cell bodies, the Purkinje cell layer and the granule cell layer and these are separated from the pial surface by a molecular layer that is largely devoid of somata. 

Purkinje cells have a number of interesting features relevant to our discussion. First, their dendrites extend only into the molecular layer, where they branch like a fan and flatten into one plane. Second, Purkinje cell axons synapse on neurons in the deep cerebellar nuclei, which are the major output cells of the cerebellum. Thus, Purkinje cells are in a powerful position to modify the output of the cerebellum. Third, Purkinje cells use GABA as a neurotransmitter so their influence on cerebellar output is inhibitory.

Purkinje cell dendrites are directly contacted by one of the two major inputs to the cerebellum. This input arises in a nucleus of the medulla referred to as the inferior olive, which functions to integrate information from muscle proprioceptors. Axons of the inferior olive are called climbing fibers because they twist around the Purkinje cell dendrites. Each Purkinje cell receives input from only one inferior olive cell but this input is very powerful. The second major input to the cerebellum arises from a variety of brain stem cell groups, including the pontine nuclei that relay information from the cerebral neocortex. These inputs, called mossy fibres, synapse on cerebellar granule cells which form a layer just below the Purkinje cells. Granule cells are very small, very tightly packed, very numerous, and send their axons up into the molecular layer. The Purkinje cells and the granule cells synapse in the molecular layer. Once the axons of the granule cells reach the molecular layer, they branch like a T with each branch, called a parallel fiber, running straight for several millimeter in a direction that intersects the plane of the Purkinje cell dendrites at a right angle (much like wires passing a telephone pole). Therefore, a single parallel fiber has only a brief encounter with any one Purkinje cell, but along its length, it encounters many. However, although a Purkinje cell receives only one synapse from each passing parallel fiber, it does so from as many as 100,000 different fibers.

*The correct answer is (A).*
**Question #07**

Which of the following is TRUE regarding the mechanisms of LTD in the cerebellum?

(A) The climbing fiber synapse with the Purkinje dendrite is weak and causes a small postsynaptic EPSP that sometimes stimulates the Purkinje cell to fire an action potential.

(B) The Purkinje cell action potential only stimulates voltage-gated sodium channels.

(C) It is mossy fiber activation that is associated with a surge of calcium into the Purkinje cell dendrite.

(D) Studies have found that when these calcium channels are blocked, LTD is also blocked.

(E) There is also a metabotropic glutamate receptor in the presynaptic Purkinje dendrite membrane.

---

### Feedback on Each Answer Choice

A. Incorrect!  
The climbing fiber synapse with the Purkinje dendrite is a very powerful input that causes a large postsynaptic EPSP that always stimulates the Purkinje cell to fire an action potential.

B. Incorrect!  
In addition to activating voltage-gated sodium channels (causing the action potential), this depolarization is powerful enough to activate voltage-gated calcium channels that exist in the membrane of the Purkinje cell dendrites.

C. Incorrect!  
It is climbing fiber activation that is associated with a surge of calcium into the Purkinje cell dendrite.

D. Correct!  
Studies have found that when these calcium channels are blocked, LTD is also blocked. This and related experiments have led to the conclusion that the critical signal provided by climbing fiber activation is a surge in calcium in the Purkinje cell dendrite.

E. Incorrect!  
The metabotropic glutamate receptor is in the postsynaptic Purkinje dendrite membrane.

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### Solution

To understand how paired stimulation of the climbing and parallel fibers leads to LTD, we need to focus on the Purkinje cell dendrite where these signals converge.

Remember that the climbing fiber synapse with the Purkinje dendrite is a very powerful input that causes a large postsynaptic EPSP that always stimulates the Purkinje cell to fire an action potential. However, in addition to activating voltage-gated sodium channels (causing the action potential), this depolarization is powerful enough to activate voltage-gated calcium channels that exist in the membrane of the Purkinje cell dendrites. Thus, climbing fiber activation is associated with a surge of calcium into the Purkinje cell dendrite. Studies have found that when these calcium channels are blocked, LTD is also blocked. This and related experiments have led to the conclusion that the critical signal provided by climbing fiber activation is a surge in calcium in the Purkinje cell dendrite.

We have already discovered that the parallel fibers release glutamate and the postsynaptic receptors in the Purkinje dendrites are AMPA receptors that are channels that mediate the EPSP by allowing sodium into the dendrite. However, there is also another type of glutamate receptor in the postsynaptic Purkinje dendrite membrane. This metabotropic glutamate receptor is coupled to a G-protein that when activated, activates the enzyme Phospholipase C. Activation of Phospholipase C leads to the production of the second messenger diacylglycerol which then activates protein kinase C. It is this PKC that phosphorylates key players involved in the internalization of AMPA receptors.

The correct answer is (D).
Question No. 8 of 10

**Instructions:** (1) Read the problem and answer choices carefully, (2) Work the problems on paper as needed, (3) Pick the answer, and (4) Review the core concept tutorial as needed.

8. Which of the following is TRUE regarding LTP in the hippocampus?

(A) Most of the experiments on the mechanisms of LTP in the hippocampus are performed on the Schaffer collateral synapses on the CA3 pyramidal neurons.

(B) Hippocampal LTP is not input specific.

(C) It requires a prolonged burst of low-frequency stimulation, to elicit LTP.

(D) The mechanisms of LTP in the CA1 neurons of the hippocampus involve excitatory synaptic transmission mediated by GABA receptors.

(E) LTP is characterized by the rise in calcium concentration activates two protein kinases: protein kinase C and calcium-calmodulin-dependent protein kinase II (also known as CaMKII).

**Feedback on Each Answer Choice**

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<td>Most of the experiments on the mechanisms of LTP in the hippocampus are performed on the Schaffer collateral synapses on the CA1 pyramidal neurons</td>
</tr>
<tr>
<td>B. Incorrect!</td>
<td>Hippocampal LTP, like cerebellar LTD, is input specific.</td>
</tr>
<tr>
<td>C. Incorrect!</td>
<td>It requires a brief burst of high-frequency stimulation, called tetanus stimulation to elicit LTP.</td>
</tr>
<tr>
<td>D. Incorrect!</td>
<td>The mechanisms of LTP in the CA1 neurons of the hippocampus involve excitatory synaptic transmission mediated by glutamate receptors.</td>
</tr>
<tr>
<td>E. Correct!</td>
<td>LTP is characterized by the rise in calcium concentration activates two protein kinases: protein kinase C and calcium-calmodulin-dependent protein kinase II (also known as CaMKII).</td>
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**Solution**

Most of the experiments on the mechanisms of LTP in the hippocampus are performed on the Schaffer collateral synapses on the CA1 pyramidal neurons in brain slice preparations. The effectiveness of the Schaffer collateral synapse is monitored by giving a bundle of presynaptic axons a brief electrical stimulus and then measuring the size of the resulting EPSP in a postsynaptic CA1 neuron. A number of properties have emerged that include: hippocampal LTP, like cerebellar LTD, is input specific and requires a brief burst of high-frequency stimulation, or tetanus stimulation to elicit LTP; co-operativity, which involves many synapses being active at the same time that the postsynaptic CA1 neuron is strongly depolarized. This last property is due to the fact that unlike the cerebellum, where a single powerful synapse can provide the critical depolarization, in the hippocampus, adequate depolarization requires that many excitatory synapses be active at the same time.

Just like in the cerebellum, the mechanisms of LTP in the CA1 neurons of the hippocampus involve excitatory synaptic transmission mediated by glutamate receptors. As with the parallel fiber-Purkinje cell synapse, sodium ions passing through the AMPA subclass of glutamate receptor cause the EPSP at the Schaffer collateral-CA1 pyramidal cell synapse. However, unlike the cerebellum, CA1 neurons also have postsynaptic NMDA receptors. These glutamate receptors have the unusual property that they conduct calcium ions but only when glutamate binds and the postsynaptic membrane is depolarized enough to displace magnesium ions that clog the channel. Thus, calcium entry through the NMDA receptor specifically signals when presynaptic and postsynaptic elements are active at the same time.

Considerable evidence now links this rise in postsynaptic calcium to the induction of LTP. LTP induction is prevented if NMDA receptors are pharmacologically inhibited or if rises in postsynaptic calcium are prevented. The rise in calcium concentration activates two protein kinases: protein kinase C and calcium-calmodulin-dependent protein kinase II (also known as CaMKII). Pharmacological inhibition of either kinase blocks the induction of LTP.

**The correct answer is (E).**
Question No. 9 of 10

**Instructions:** (1) Read the problem and answer choices carefully, (2) Work the problems on paper as needed, (3) Pick the answer, and (4) Review the core concept tutorial as needed.

**Question #09**

9. Which of the following is FALSE regarding CaMKII?

(A) The CaMKII protein consists of a regulatory and a catalytic domain with a hinge in the middle.

(B) When the kinase is ‘off’ the catalytic domain is covered by phosphorylation.

(C) It is the catalytic domain that performs the phosphorylation and the regulatory domain that interacts with the second messenger.

(D) When the second messenger is present, the kinase protein undergoes a conformational change and the catalytic domain is closed.

(E) The hinge can stay open due to dephosphorylation using a phosphatase.

**Feedback on Each Answer Choice**

A. Incorrect!
It is true that as with many kinase enzymes, the CaMKII protein consists of a regulatory and a catalytic domain with a hinge in the middle.

B. Correct!
When the kinase is ‘off’ the regulatory domain covers the catalytic domain so that it cannot phosphorylate anything.

C. Incorrect!
It is true that it is the catalytic domain that performs the phosphorylation and the regulatory domain that interacts with the second messenger.

D. Incorrect!
When the second messenger is present, the kinase protein undergoes a conformational change and the catalytic domain is open.

E. Incorrect!
CaMKII is an autophosphorylating protein kinase; each subunit within the CaMKII molecule can be phosphorylated by a neighboring subunit. The consequence of subunit phosphorylation is that the hinge stays open.

**Solution**

Recall that calcium entry into the postsynaptic cell and activation of CaMKII are required for the induction of LTP in CA1. Research has shown that CaMKII stays ‘on’ long after calcium concentrations have fallen back to a low level. As with many kinase enzymes, the CaMKII protein consists of a regulatory and a catalytic domain with a hinge in the middle. It is the catalytic domain that performs the phosphorylation and the regulatory domain that interacts with the second messenger. When the kinase is ‘off’ the regulatory domain covers the catalytic domain so that it cannot phosphorylate anything. However, when the second messenger is present, the kinase protein undergoes a conformational change and the catalytic domain is open. When the second messenger is removed, the kinase goes back to its original shape and once again is ‘off’. After LTP however, it appears that the kinase protein fails to return completely to its original shape. The exposed catalytic region continues to phosphorylate CaMKII substrates.

How is the hinge of the protein kinase molecule kept open? The answer lies in the fact that CaMKII is an autophosphorylating protein kinase; each subunit within the CaMKII molecule can be phosphorylated by a neighboring subunit. The consequence of subunit phosphorylation is that the hinge stays open. If the initial activation of CaMKII by calcium-calmodulin is sufficiently strong, autophosphorylation will occur at a faster rate than dephosphorylation, and the molecule will be switched ‘on’. Persistent activity of CaMKII could contribute to the maintenance of synaptic potentiation, for example, by keeping the postsynaptic AMPA receptors phosphorylated. The general idea that an autophosphorylating kinase could store information at the synapse is called the molecular switch hypothesis.

**The correct answer is (B).**
Question No. 10 of 10

**Instructions:** (1) Read the problem and answer choices carefully, (2) Work the problems on paper as needed, (3) Pick the answer, and (4) Review the core concept tutorial as needed.

<table>
<thead>
<tr>
<th><strong>Question #10</strong></th>
<th>10. Which of the following is TRUE regarding the role of new protein synthesis in memory?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(A) If brain protein synthesis is inhibited at the time of training, the animals learn normally but fail to remember when tested days later.</td>
</tr>
<tr>
<td></td>
<td>(B) Studies show that CREB is not involved in memory consolidation.</td>
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<tr>
<td></td>
<td>(C) There is no requirement for new protein synthesis during the period of memory consolidation.</td>
</tr>
<tr>
<td></td>
<td>(D) The memories become increasingly open to the inhibition of protein synthesis as the interval between training and the injection of inhibitor is increased.</td>
</tr>
<tr>
<td></td>
<td>(E) CREB stands for “cyclic ATP reporting electron binding”.</td>
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</tbody>
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<td><strong>A. Correct!</strong></td>
<td>It is true that if brain protein synthesis is inhibited at the time of training, the animals learn normally but fail to remember when tested days later.</td>
</tr>
<tr>
<td><strong>B. Incorrect!</strong></td>
<td>It was in 1994 that a seminal study showed that CREB regulates the gene expression required for memory consolidation in the fruit fly Drosophila.</td>
</tr>
<tr>
<td><strong>C. Incorrect!</strong></td>
<td>Studies indicate a requirement for new protein synthesis during the period of memory consolidation.</td>
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<td><strong>D. Incorrect!</strong></td>
<td>The memories become increasingly resistant to the inhibition of protein synthesis as the interval between training and the injection of inhibitor is increased.</td>
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<td>CREB stands for “cyclic AMP response element binding”.</td>
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</tbody>
</table>

| **Solution** | The possible role of new protein synthesis in memory has been investigated extensively since the introduction of drugs in the 1960’s that selectively inhibit the assembly of protein from messenger RNA. Protein synthesis inhibitors can be injected into the brains of experimental animals as they are trained to perform a task and deficits in learning and memory can be assessed. These studies reveal that if brain protein synthesis is inhibited at the time of training, the animals learn normally but fail to remember when tested days later. A deficit in long-term memory is also often observed if the inhibitors are injected shortly after training. However, the memories become increasingly resistant to the inhibition of protein synthesis as the interval between training and the injection of inhibitor is increased. These findings indicate a requirement for new protein synthesis during the period of memory consolidation, when short-term memories are converted into long-term ones.  
Recall that the very first step in protein synthesis is the generation of an mRNA transcript of a gene. This process of gene expression is regulated by transcription factors in the nucleus. One transcription factor is called the cyclic AMP response element binding protein, or CREB. CREB is a protein that binds to specific segments of DNA called cyclic AMP response elements (CREs) and functions to regulate the expression of neighboring genes. It was in 1994 that a seminal study showed that CREB regulates the gene expression required for memory consolidation in the fruit fly Drosophila. Since then, other studies have found the same effect in other organisms such as Aplysia. Modulation of gene expression by CREB offers a molecular mechanism that can control the strength of a memory.  
**The correct answer is (A)** |

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