

# **Molecular Biology of Memory Storage:**

## **The Persistence of Memory**

# **The Study of Memory Has Two Parts:**

## **(1) The *Systems* Problem of Memory:**

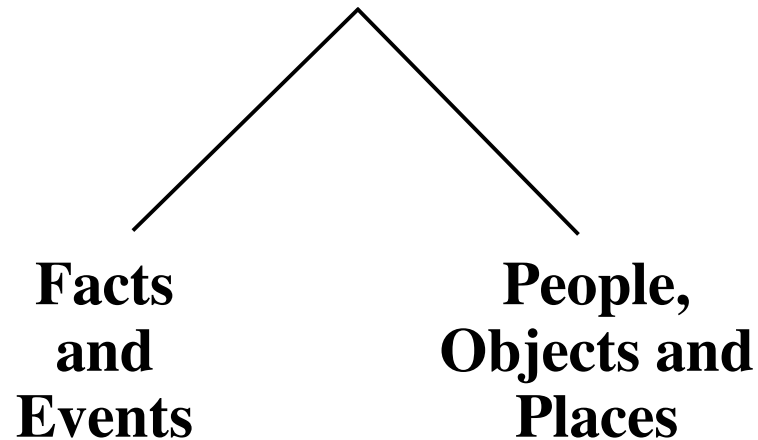
Where in the brain is memory stored?

## **(2) The *Molecular* Problem of Memory:**

How is memory stored at each site?

# There are Two Major Forms of Long-Term Memory

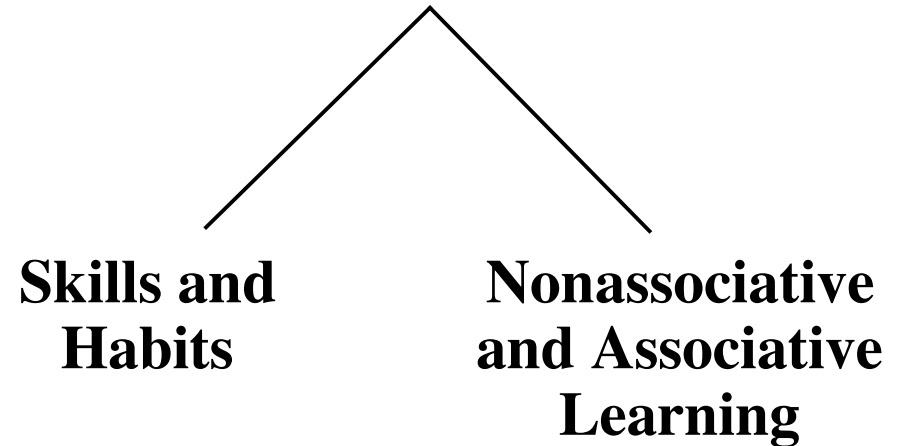
## Explicit (Declarative)



**Medial Temporal Lobe  
Hippocampus**

**Requires Conscious Attention**

## Implicit (Procedural)



**Amygdala, Striatum,  
Cerebellum, Reflex Pathways**

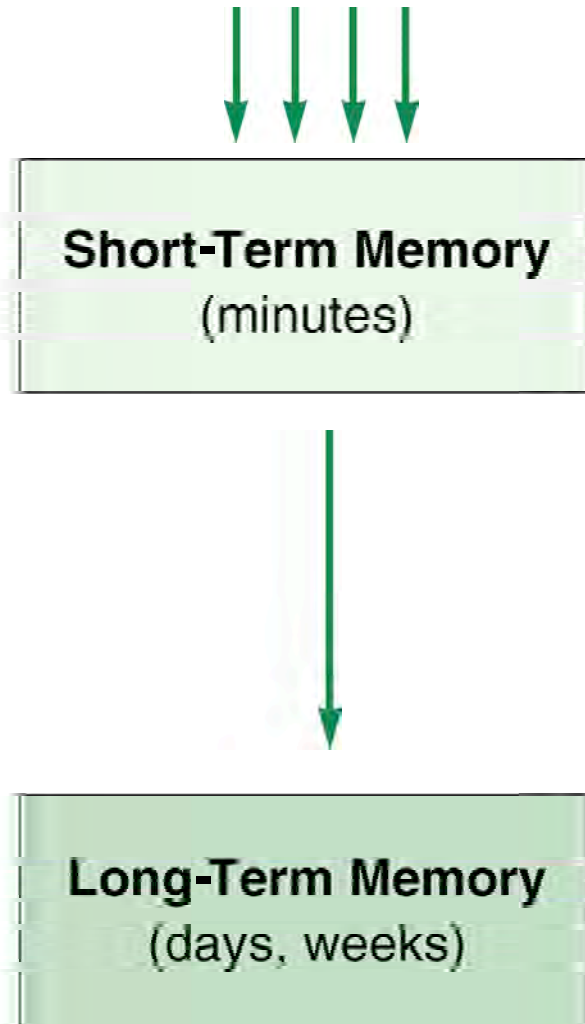
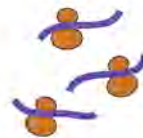
**Does Not Require Conscious Attention**

# Implicit and Explicit Memory Share 3 Features in Common

**1 There are Stages to Memory Storage**

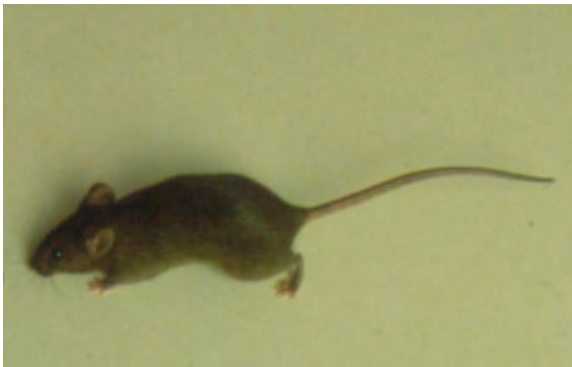
**2 Repetition Converts Short- to Long-Term Memory**

**3 Long-Term Memory Requires New Protein Synthesis**



# There are Two Major Forms of Long-Term Memory

## Explicit (Declarative)

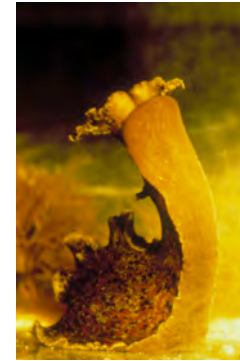


**Place:  
Spatial Memory**

**Medial Temporal Lobe  
Hippocampus**

**Requires Conscious Attention**

## Implicit (Procedural)

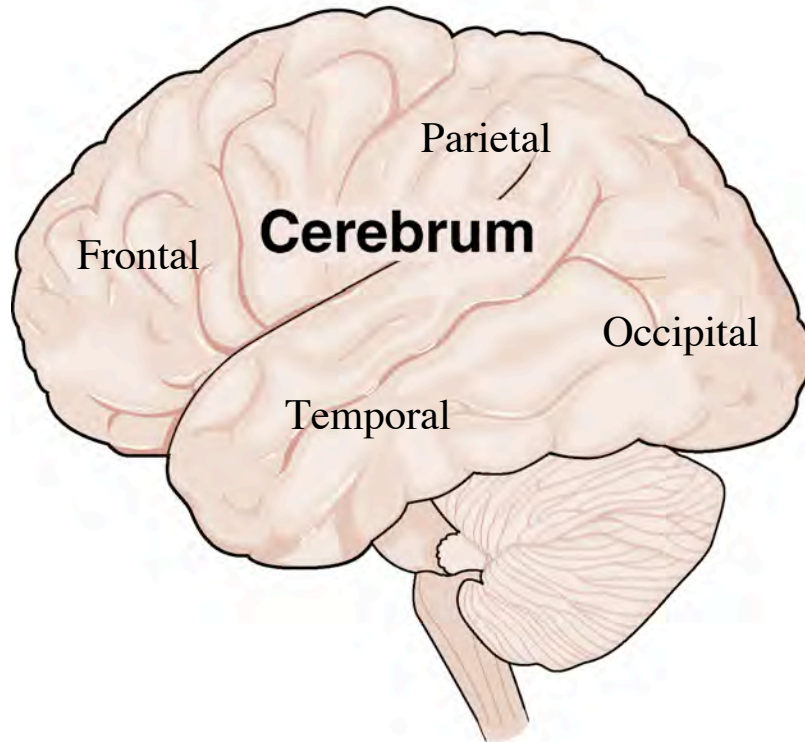


**Nonassociative Learning:  
Learned Fear (Sensitization)**

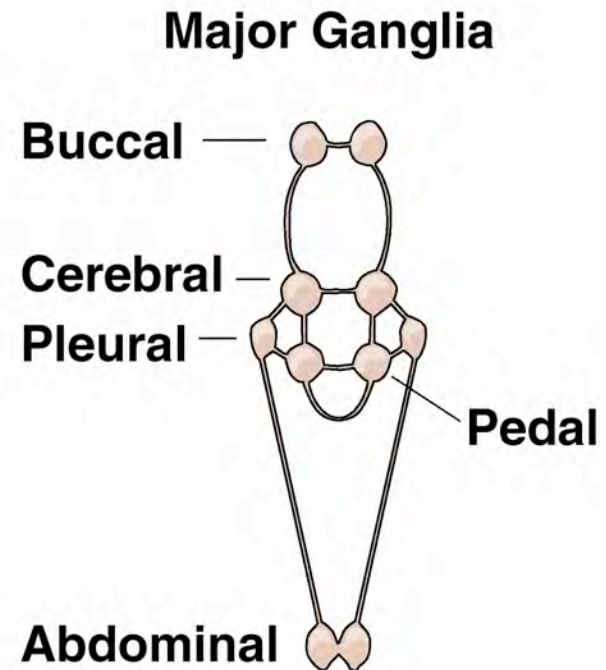
**Reflex Pathways**

**Does Not Require Conscious Attention**

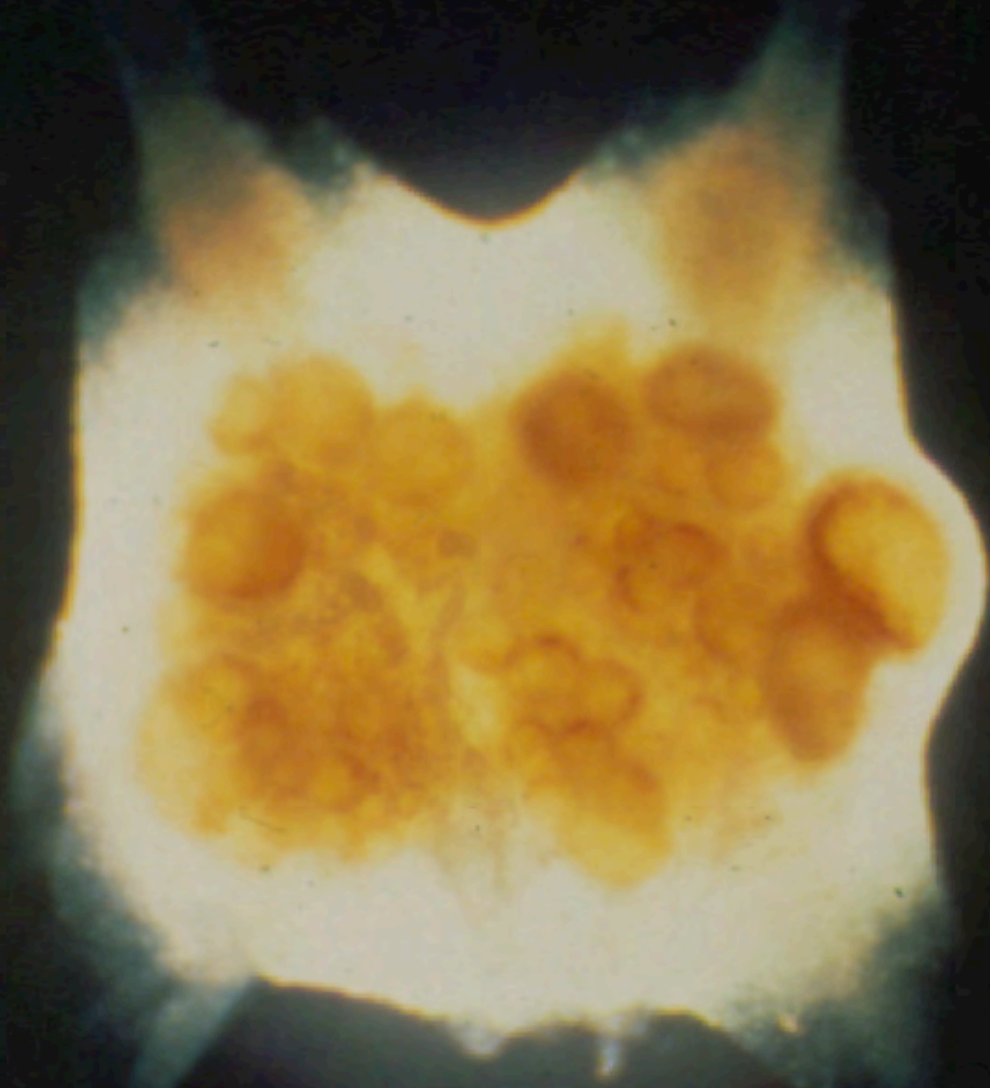
**The Human Brain  
is complex:  
 $10^{12}$  Neurons**



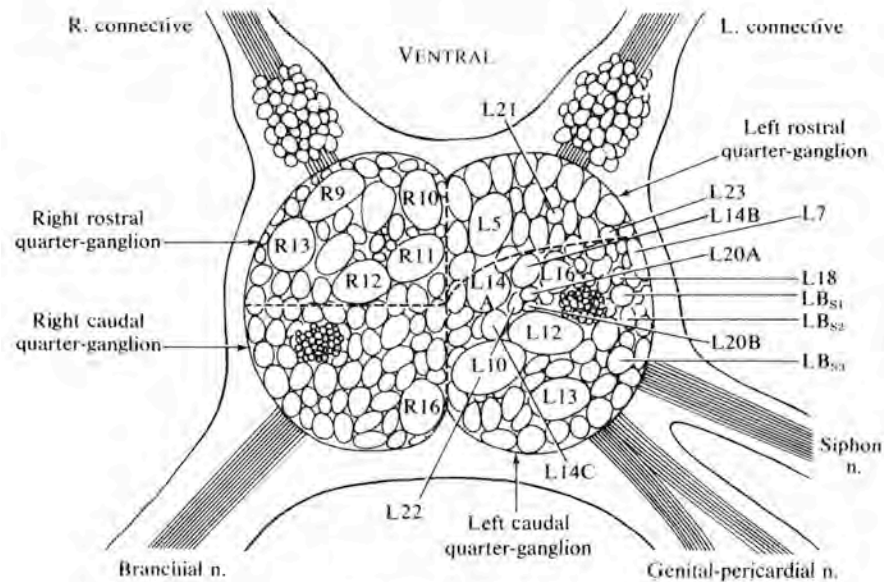
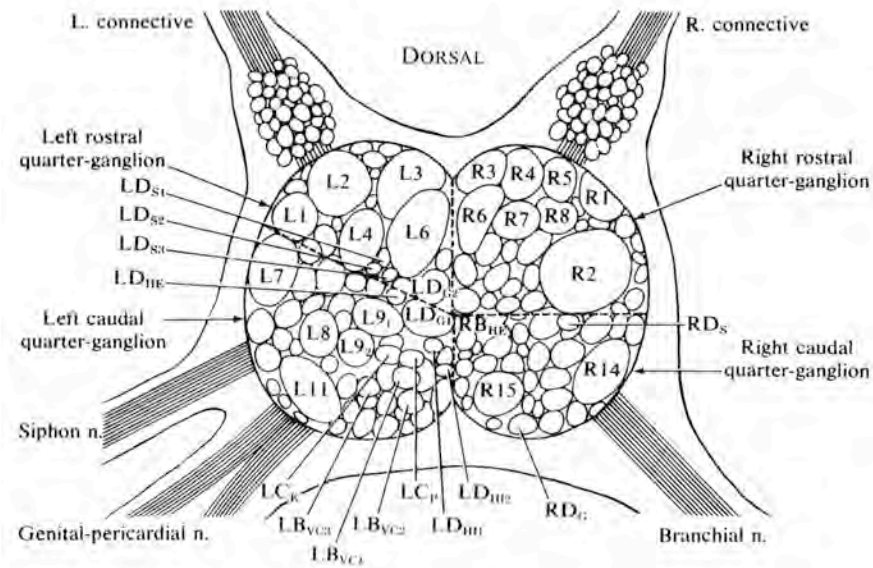
**The *Aplysia* Brain  
is simple:  
 $2 \times 10^4$  Neurons**



# Abdominal Ganglion of Aplysia

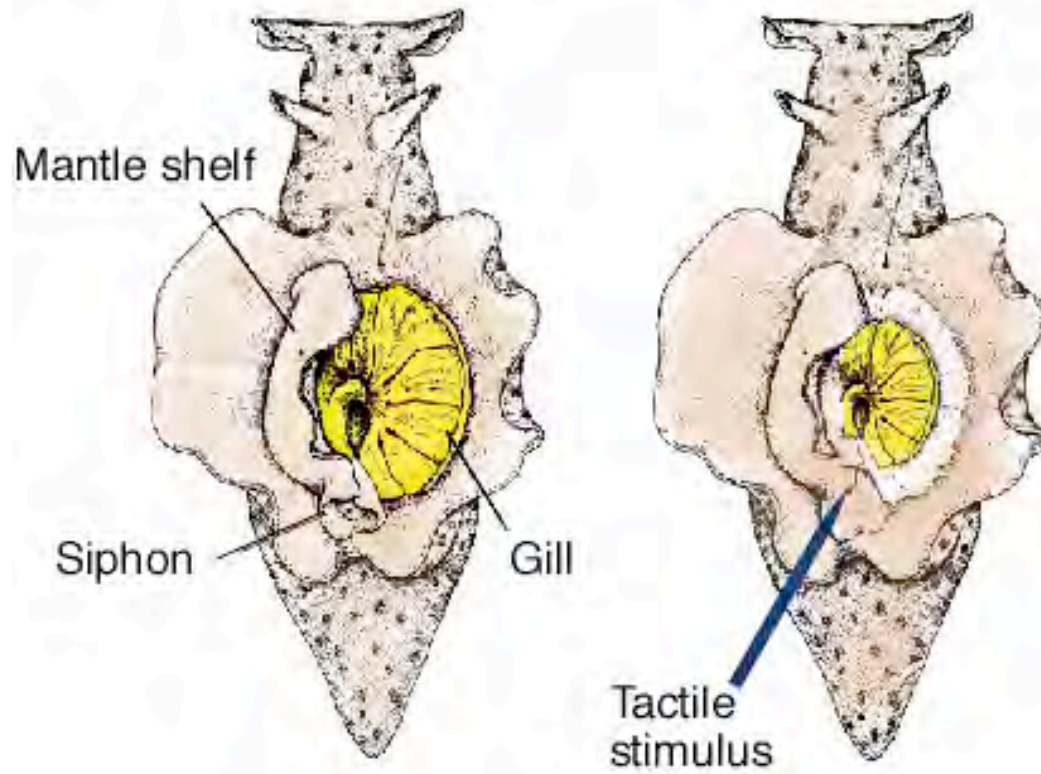


# Identified Cells and Clusters of the Abdominal Ganglion

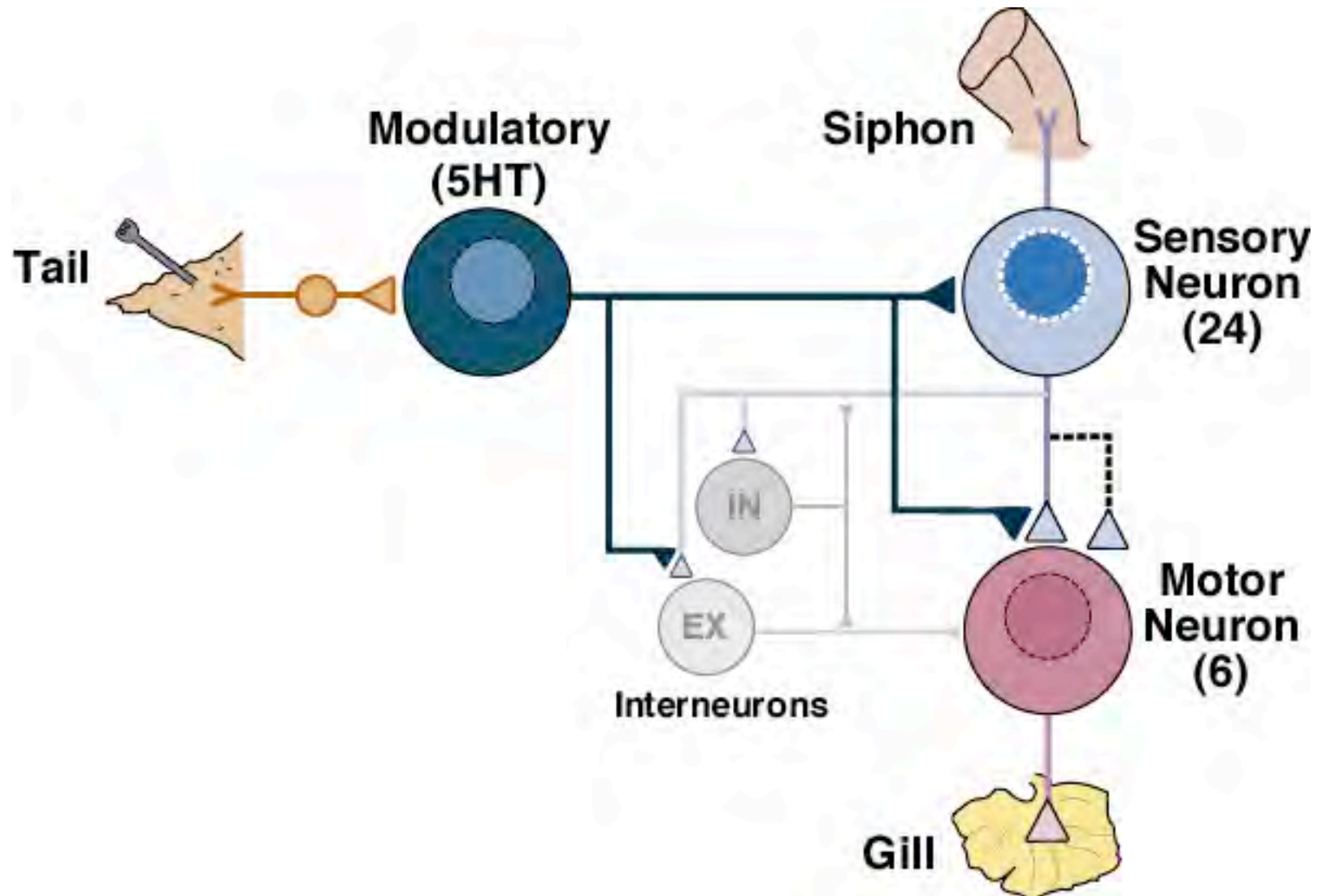


*Aplysia californica*

## Gill Withdrawal Reflex

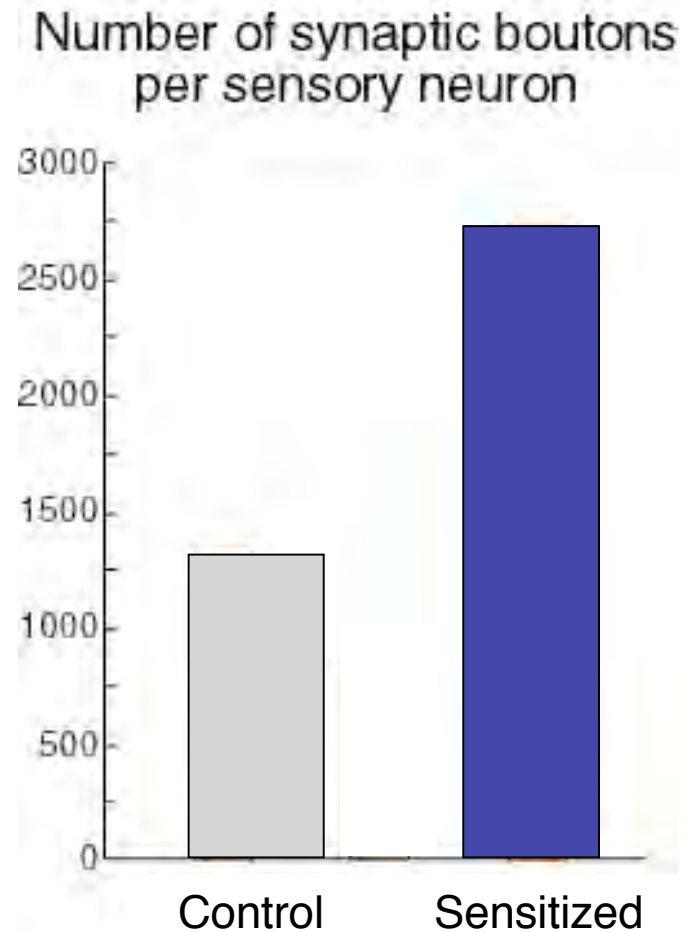
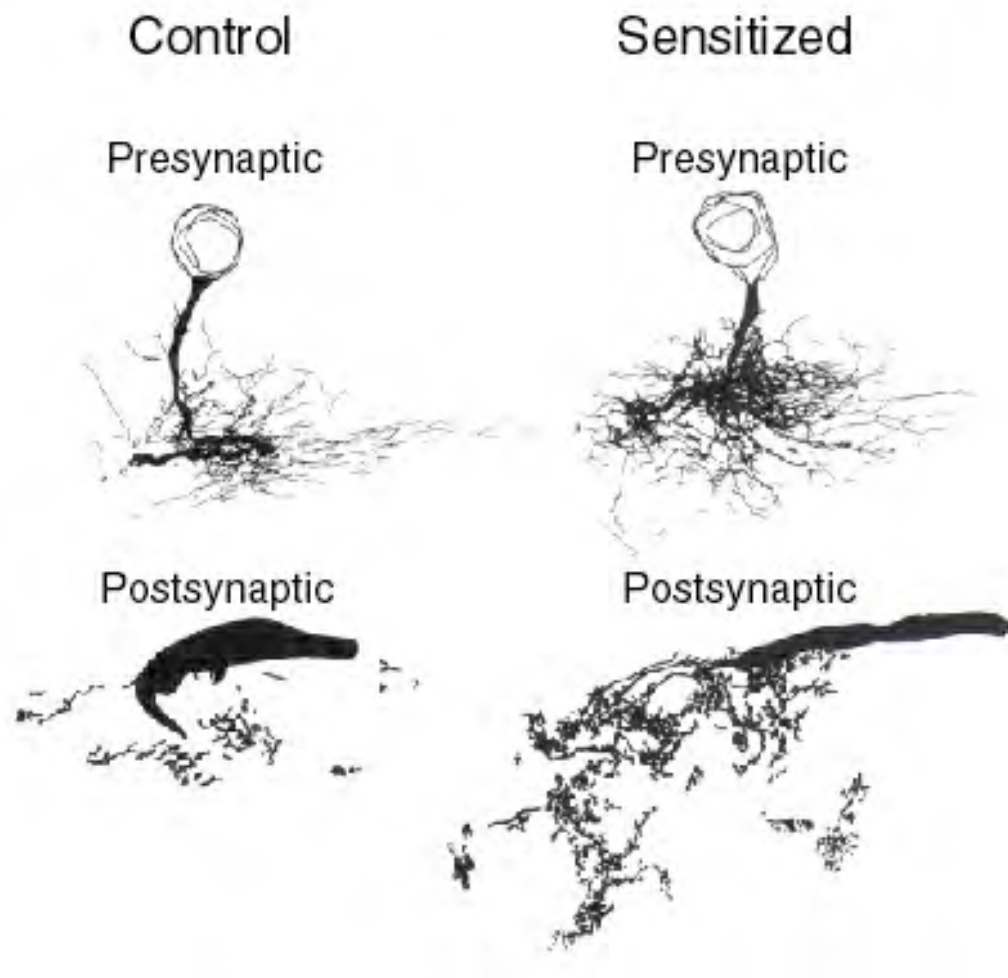


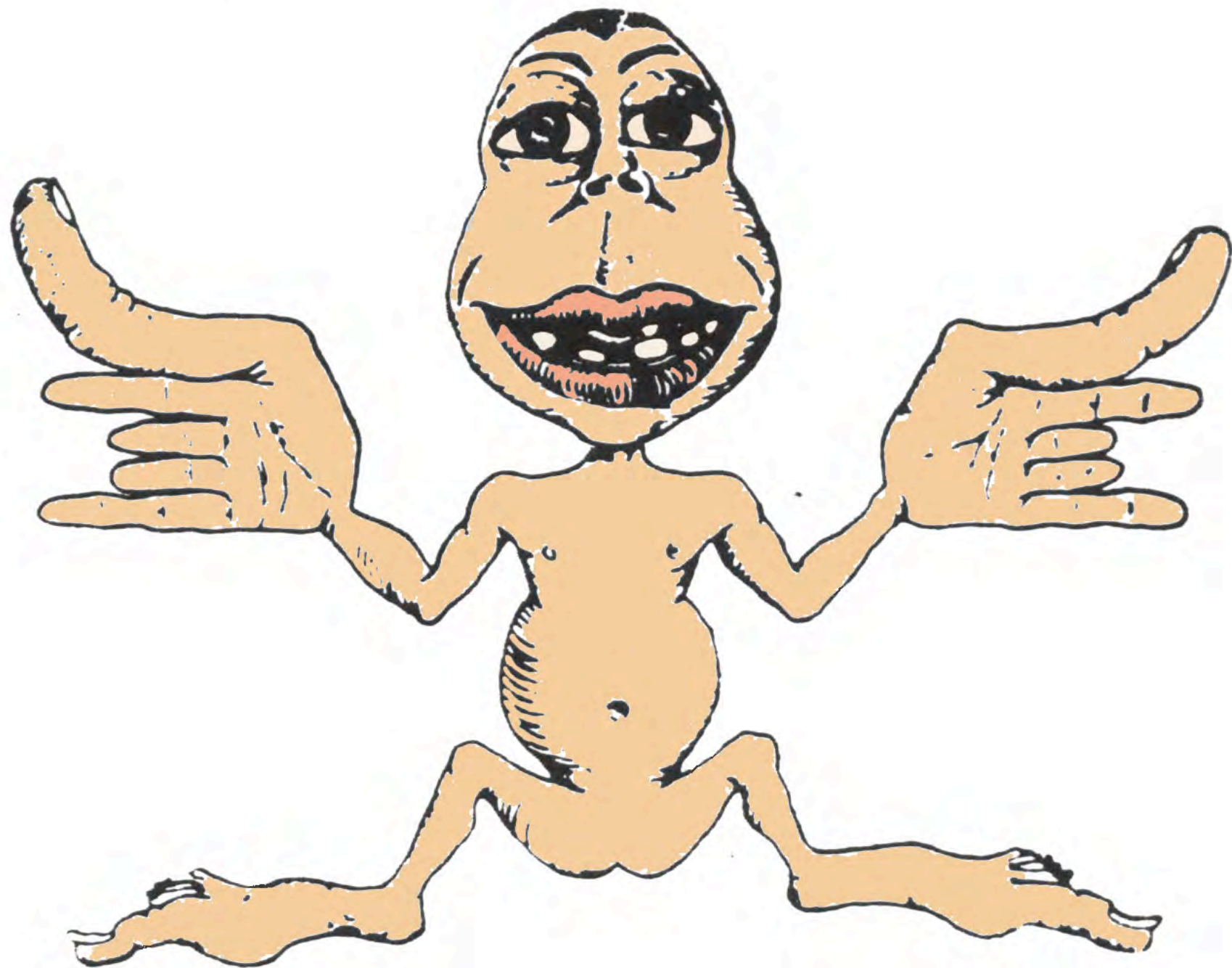
**The Gill Withdrawal Reflex has a Simple Stereotypical Neural Circuit. Repetition of Sensitization Training Leads to Altered Gene Expression and the Growth of New Synaptic Connections.**



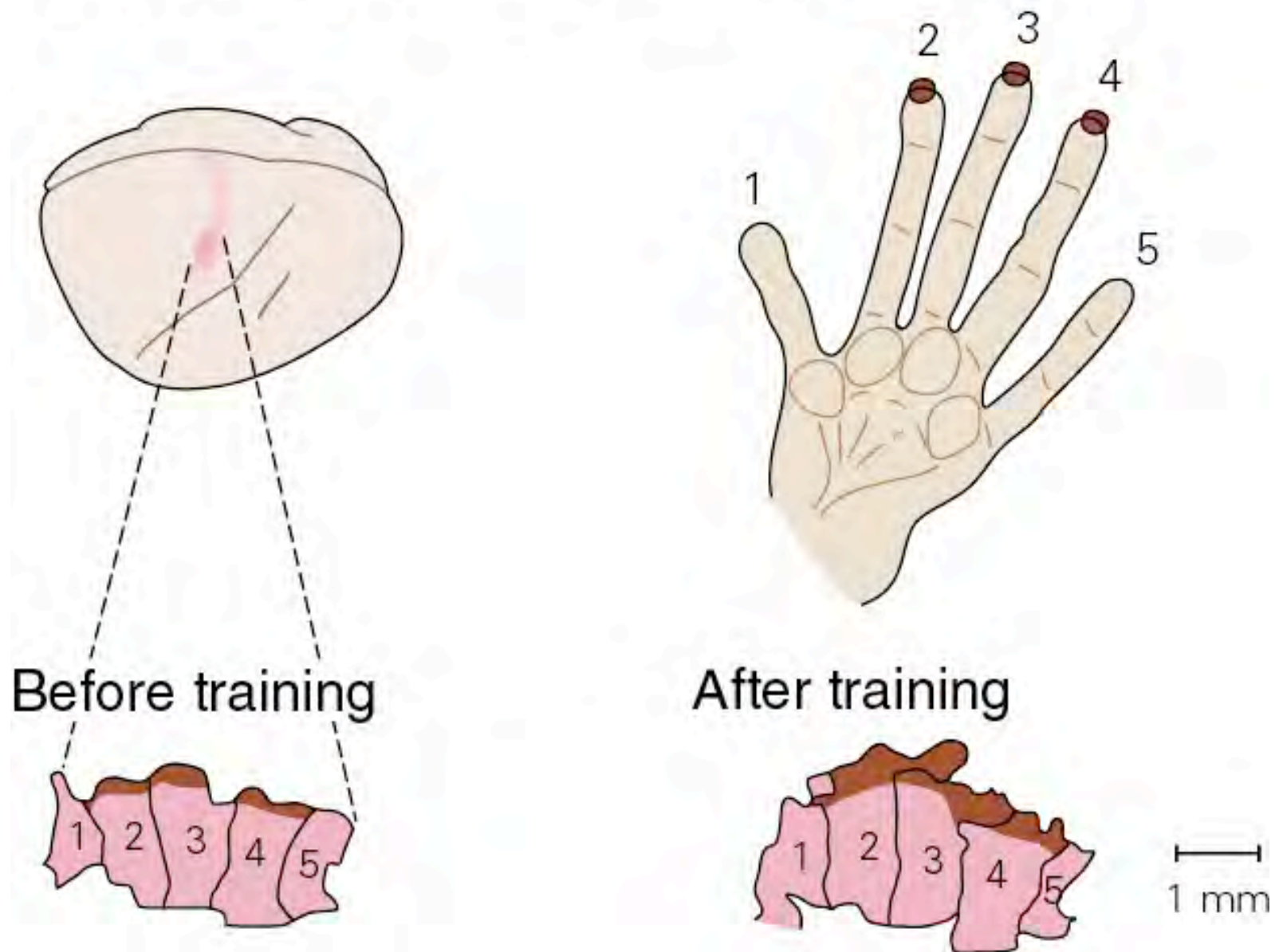


# Sensitization Produces Both Pre- and Postsynaptic Structural Changes in the Intact Animal (HRP)





# Cortical Representation of Fingers



# There are Two Major Forms of Long-Term Memory

**Explicit (Declarative)**

**Implicit (Procedural)**

**Place:  
Spatial Memory**

**Nonassociative Learning:  
Learned Fear**

**Medial Temporal Lobe  
Hippocampus**

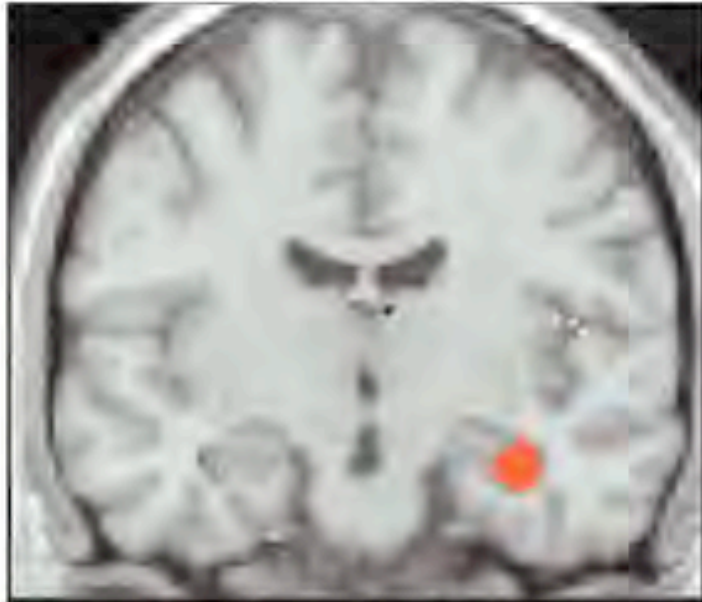
**Reflex Pathways**

**Requires Conscious Attention**

**Does Not Require Conscious Attention**

# Hippocampus of Humans Encodes Space (Mental Time Travel)

Route from Hyde Park  
to Primrose Hill



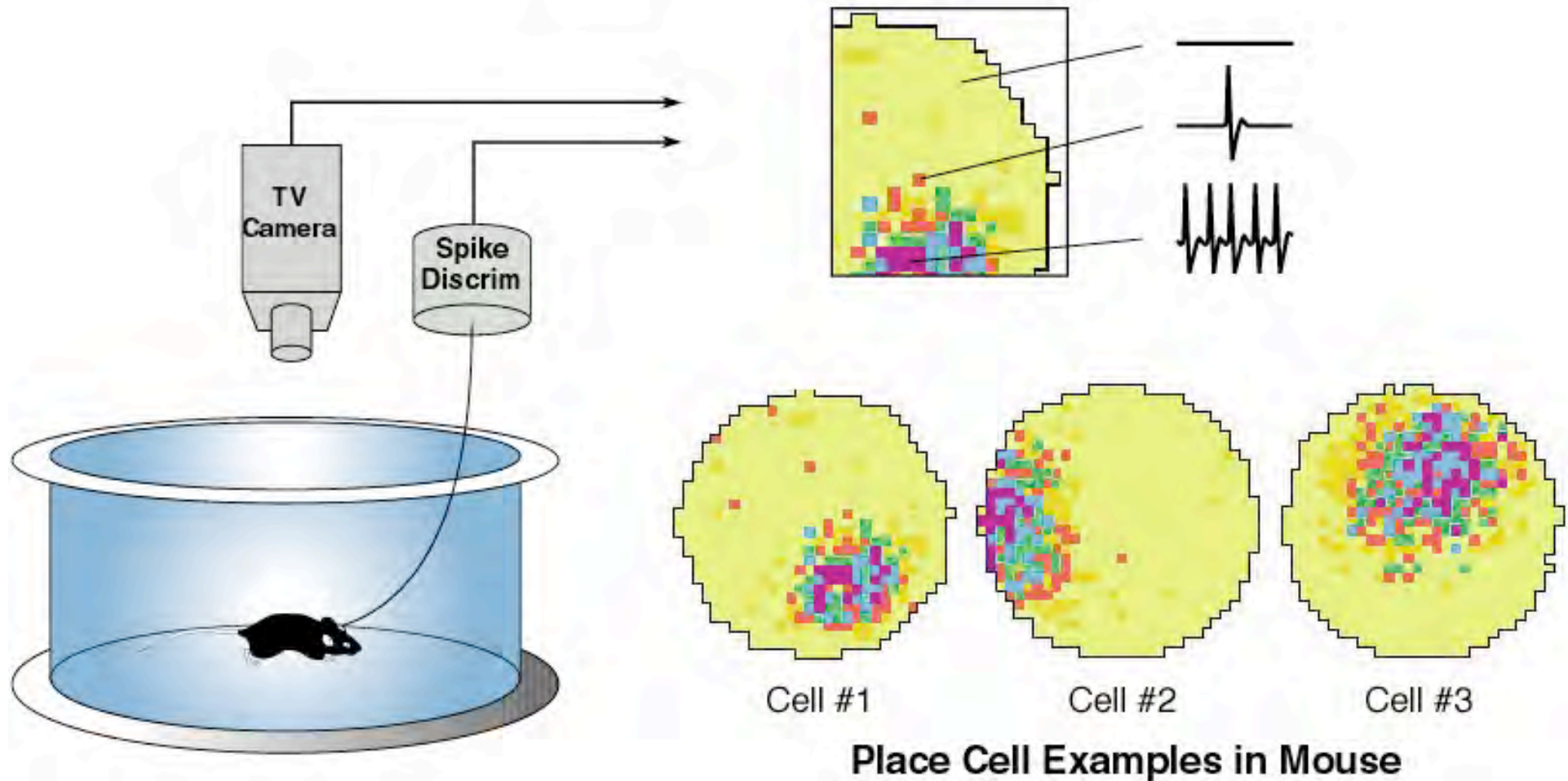
# Hippocampus of Mice Also Encodes Space



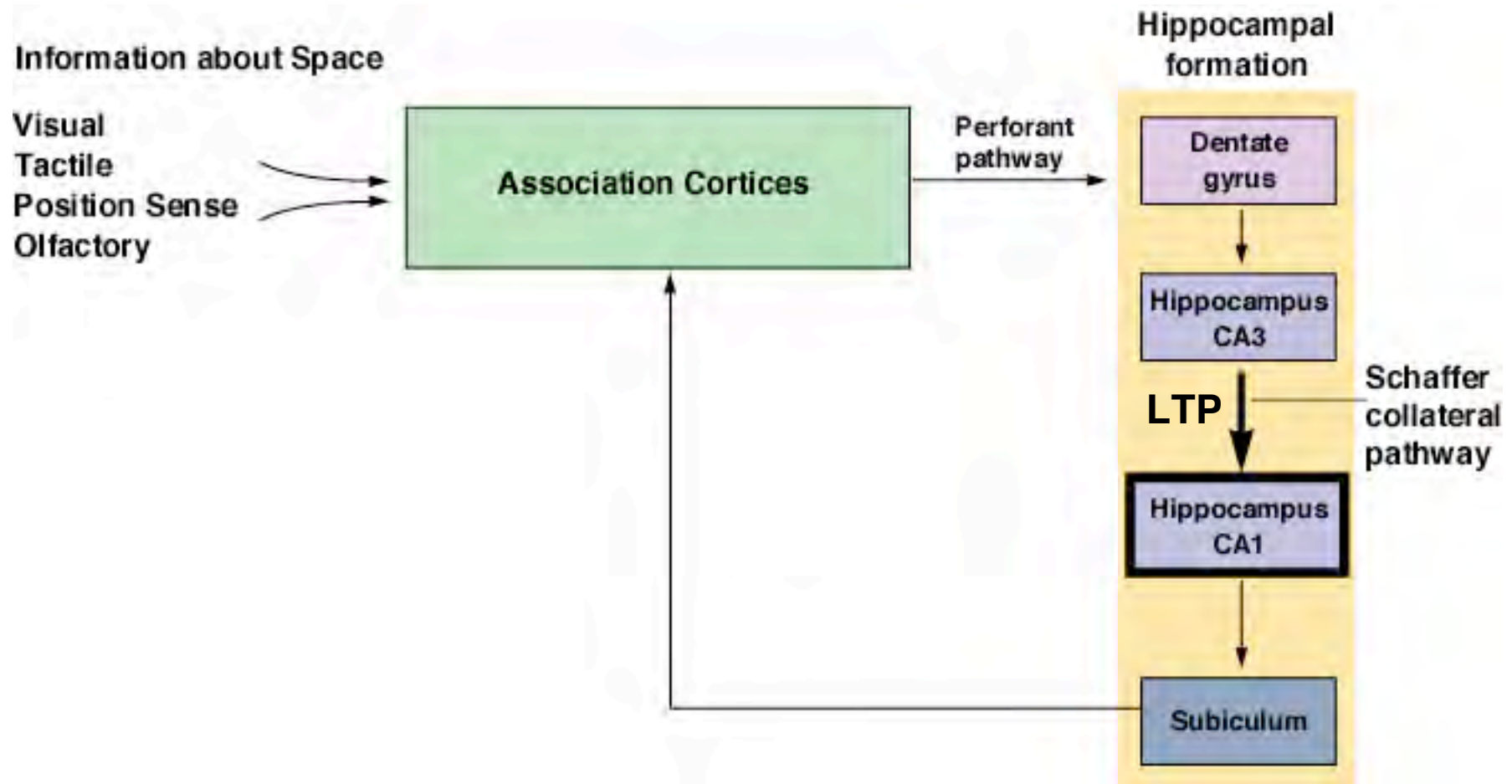
# Multi-Sensory Information About Spatial Memory is Brought Together in the CA1 Region of the Hippocampus



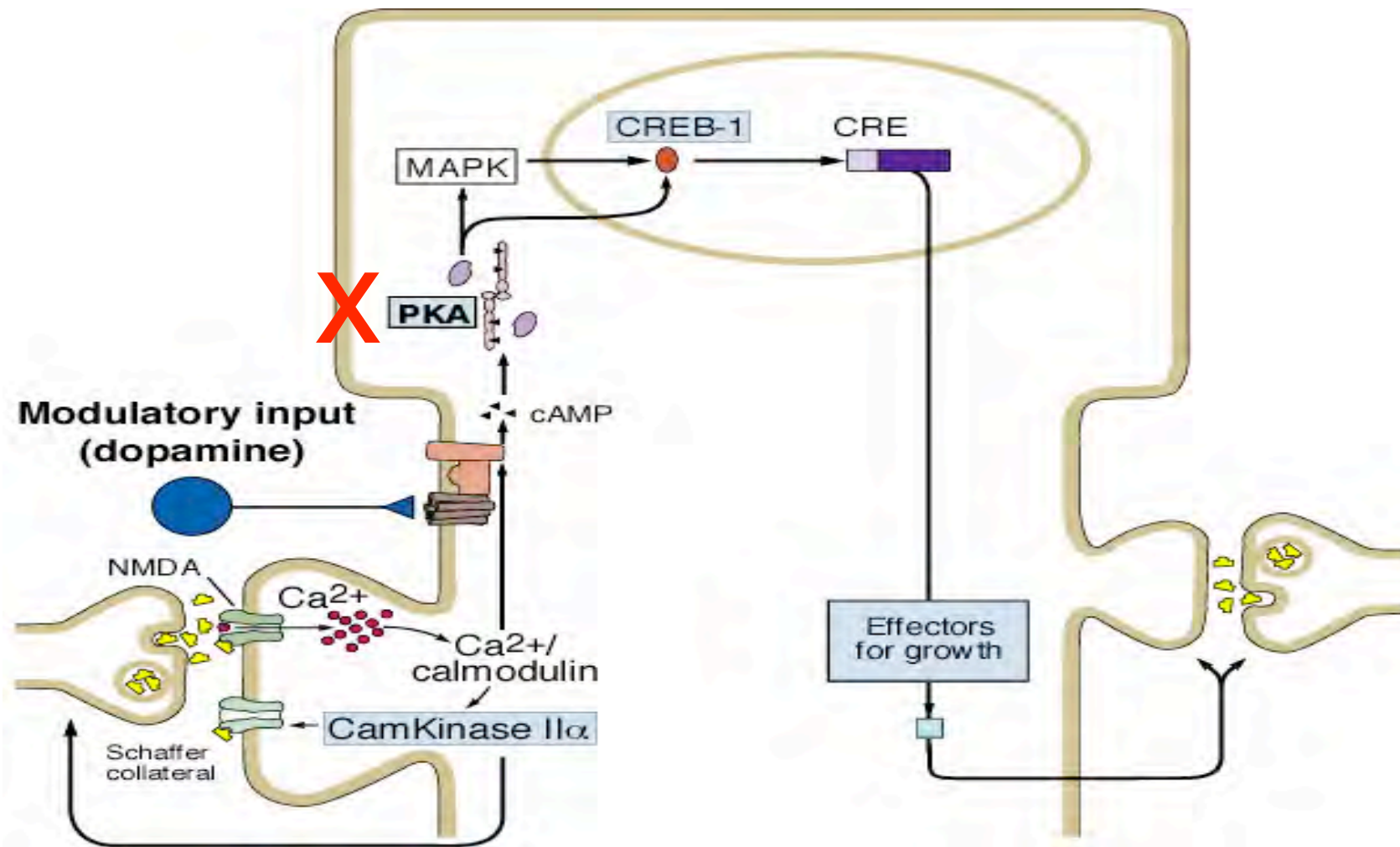
# Relating Molecular Signaling to the Cognitive Map for Space: The Hippocampal Pyramidal Cells in the CA1 Region Encode Space



# Is Synaptic Plasticity in the Hippocampal Ca1 Region Important for Learning a Spatial Representation and for Storing a Spatial Memory?

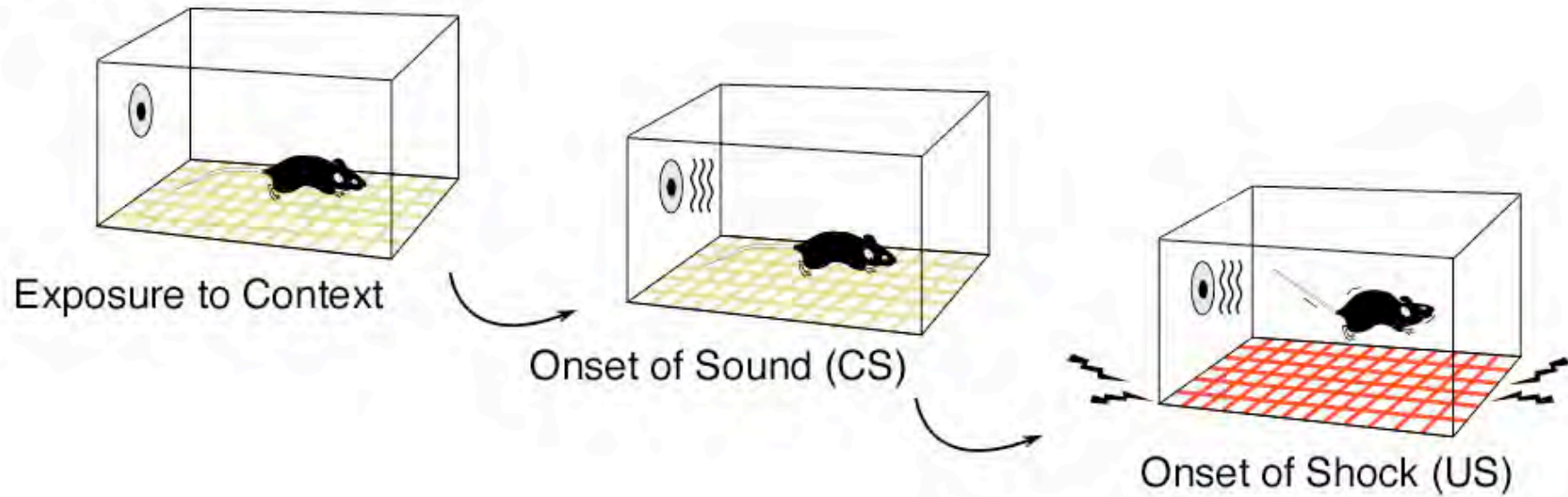


# The Long-Term Stability of Hippocampal Synaptic Plasticity( Long Term Potentiation) Requires PKA



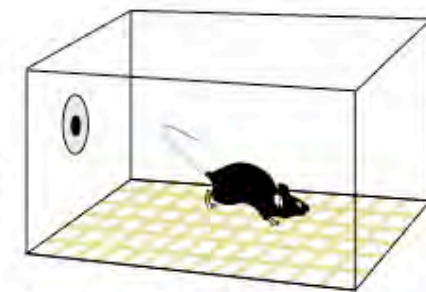
# Contextual Conditioning

## Training



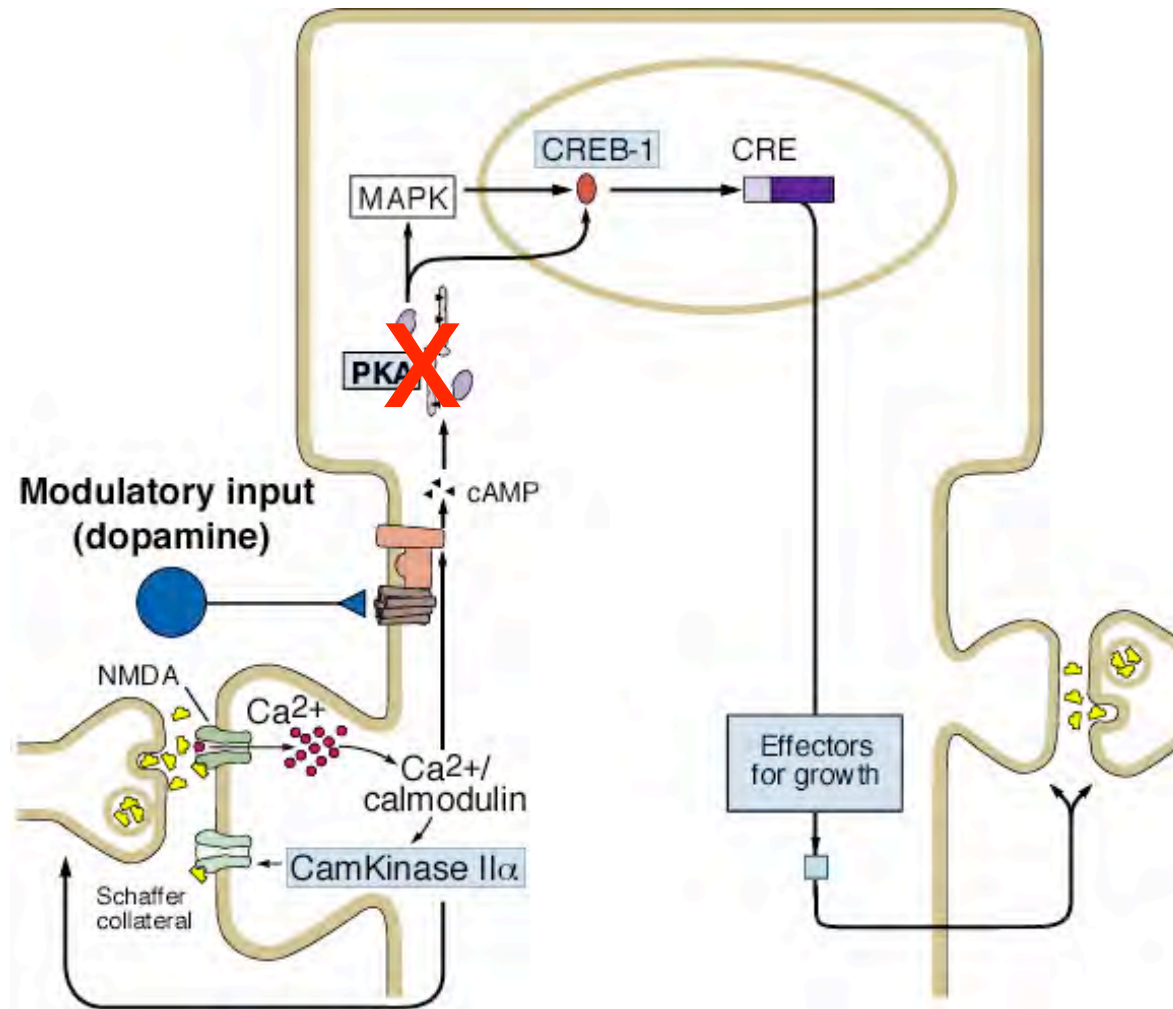
## Testing

1 hour and 24 hours

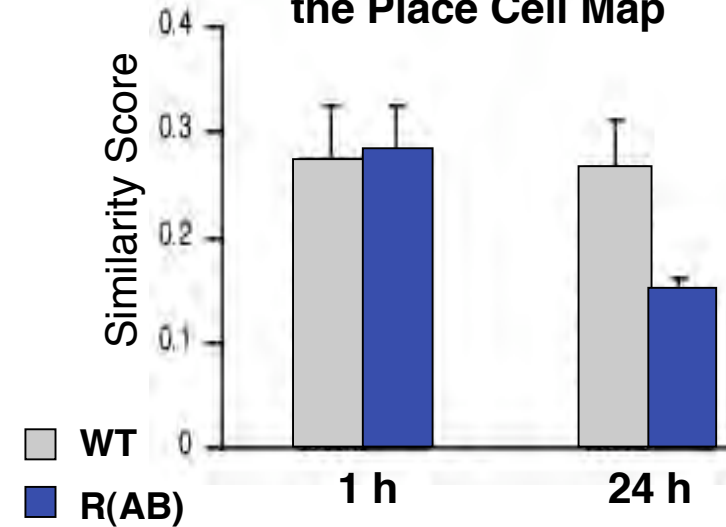


Same Context

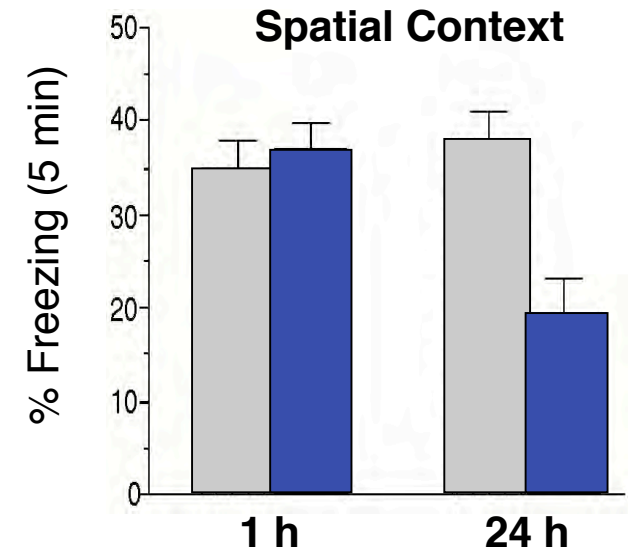
# Both the Long-Term Memory for Space and the Long-Term Stability of the Place Cell Map Require PKA



Long-Term Stability of the Place Cell Map



Long-Term Memory of Spatial Context



# **How Does Attention Affect the Internal Representation of Space?**

# Is Attention Important to Form the Spatial Map or to Stabilize and Perpetuate it?

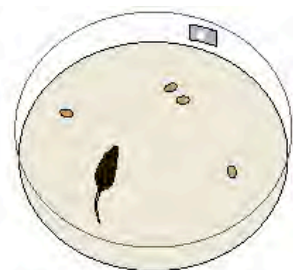
## Four Degrees of Attention

1 No Task



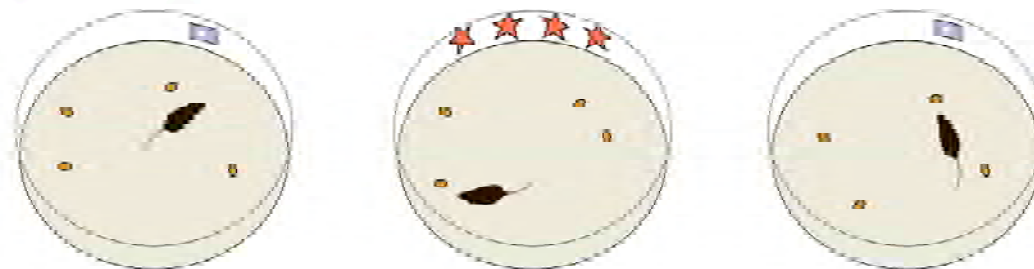
Not hungry  
No food

2 Foraging

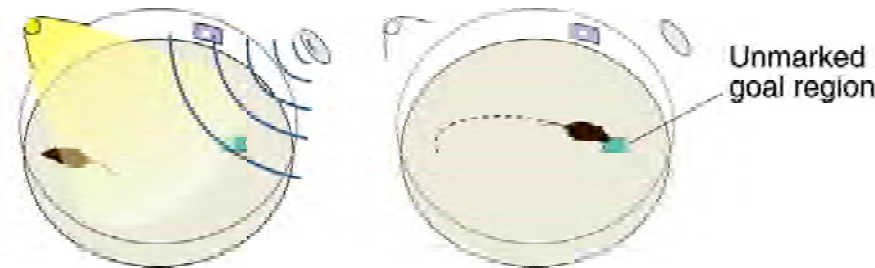


Hungry Mouse  
Random food drops

3 Discriminating

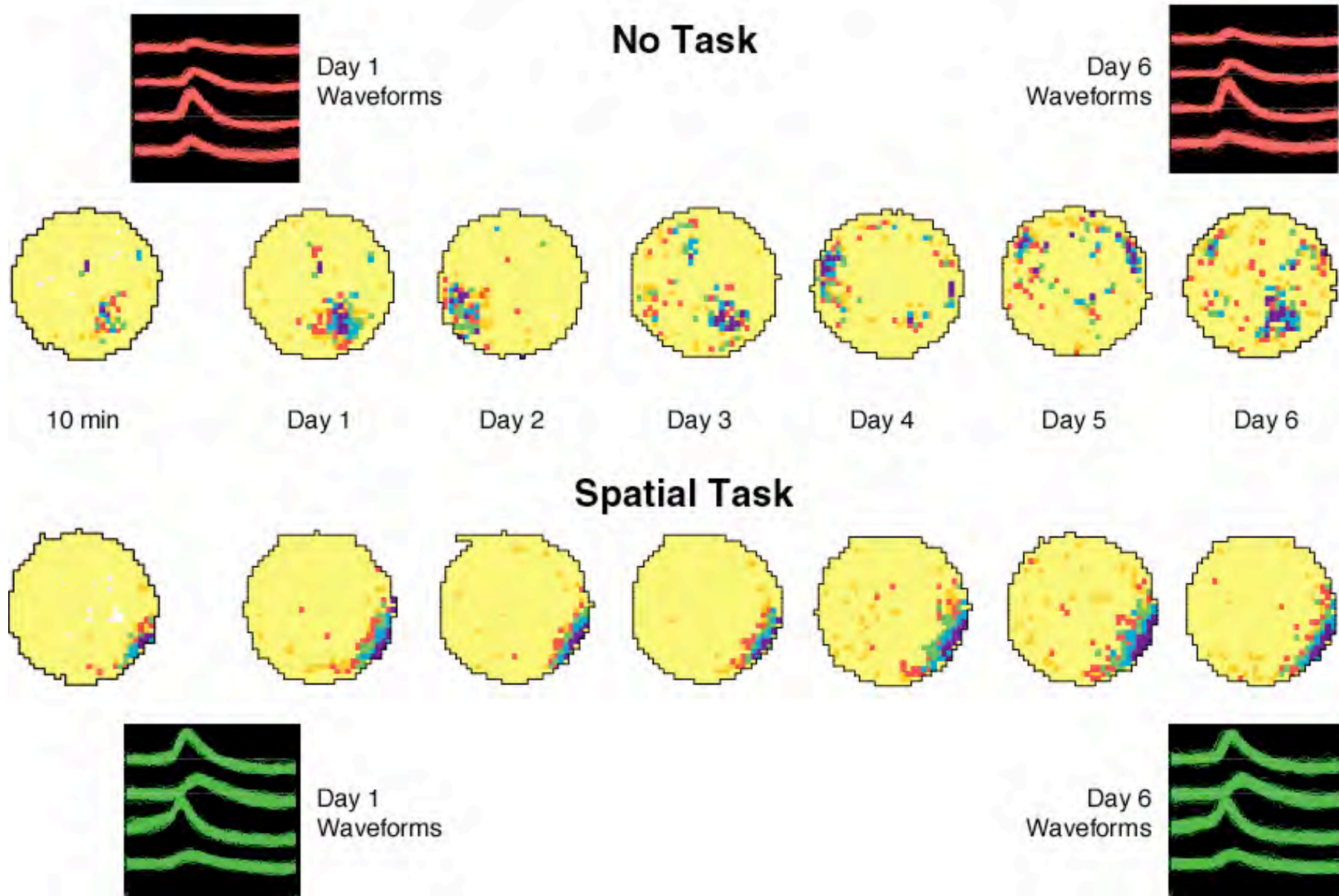


4 Spatial Task



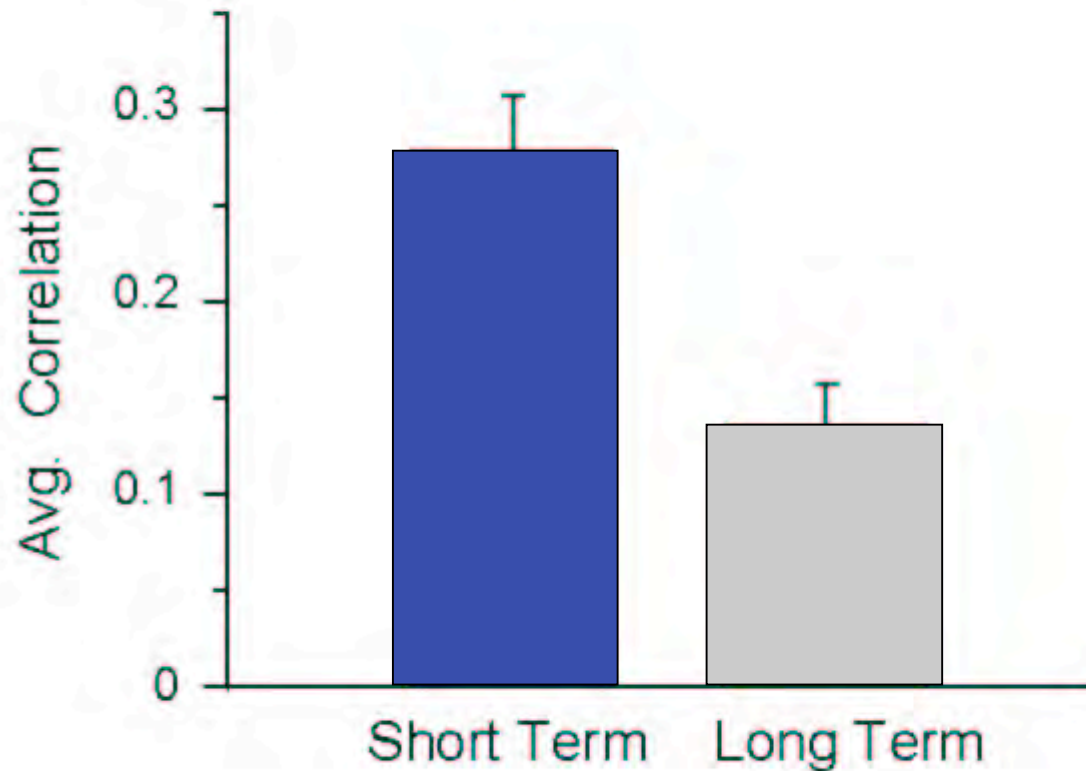
Noxious  
environment  
Mouse able to  
shut off stimuli

# Place Field Stability Depends on Task Requirements

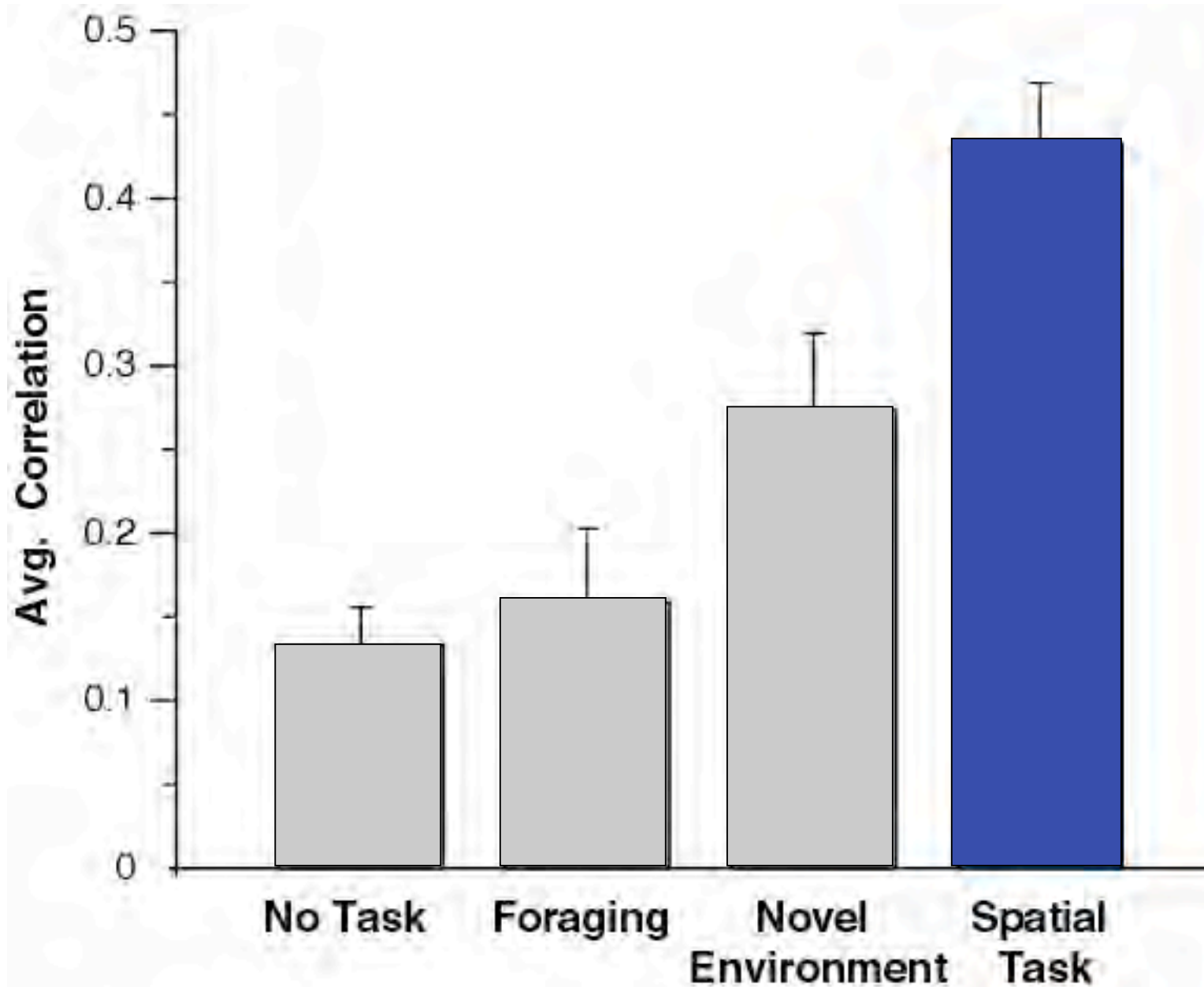


# Short Term Stability of Place Cells Does Not Require Selective Attention

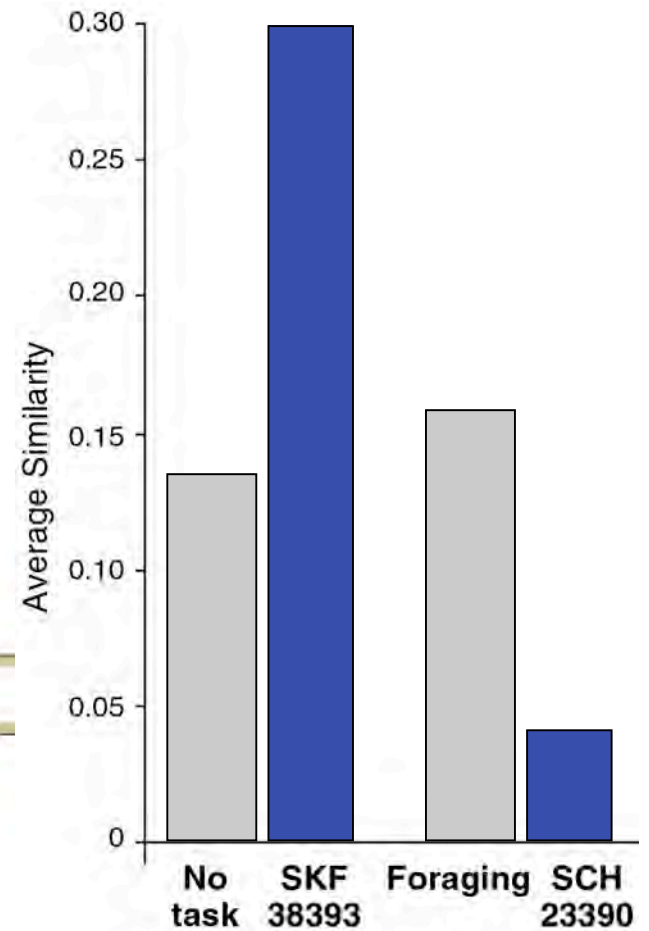
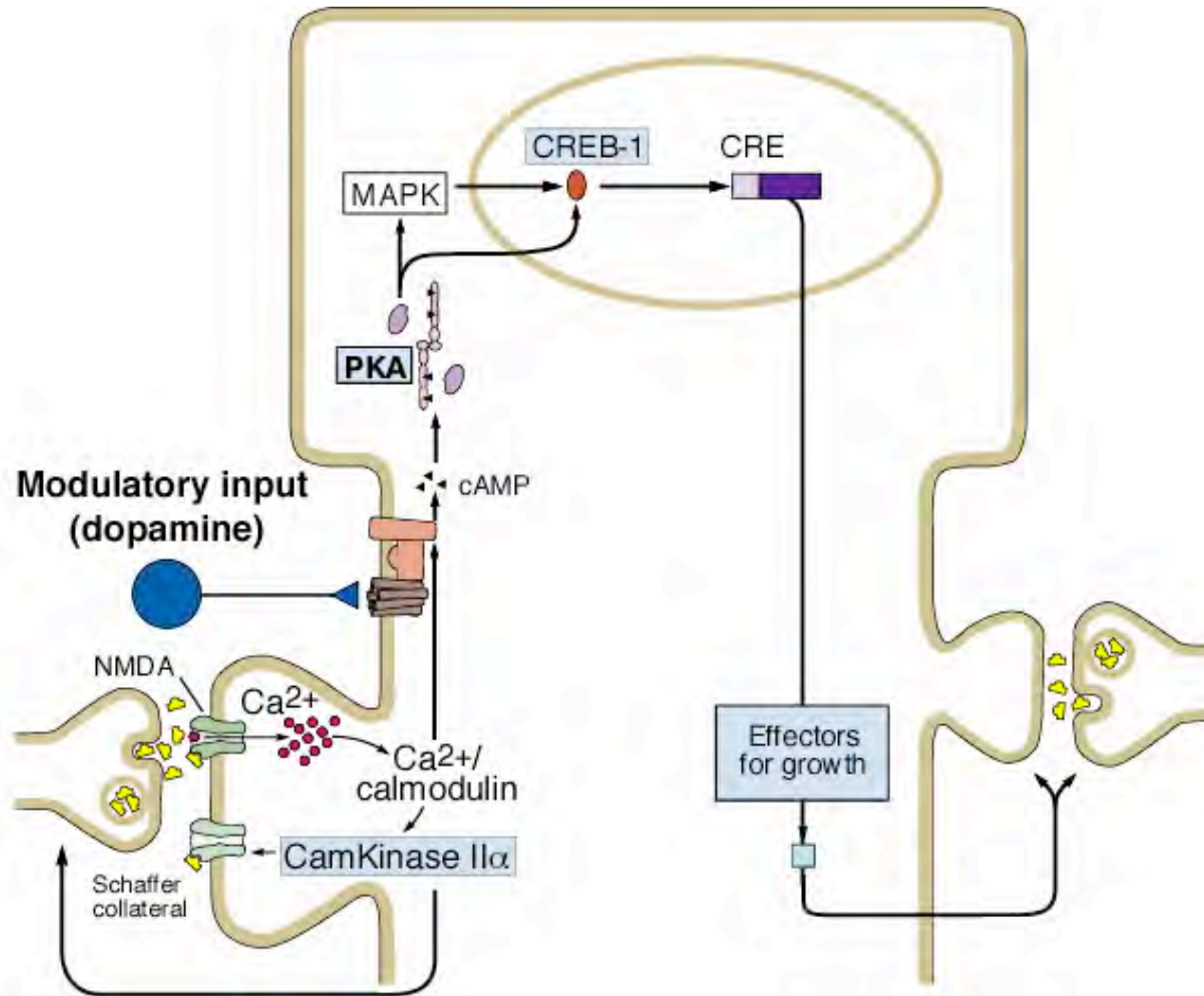
## Short vs. Long Term Instability



# Long Term Place Cell Stability Requires Selective Attention

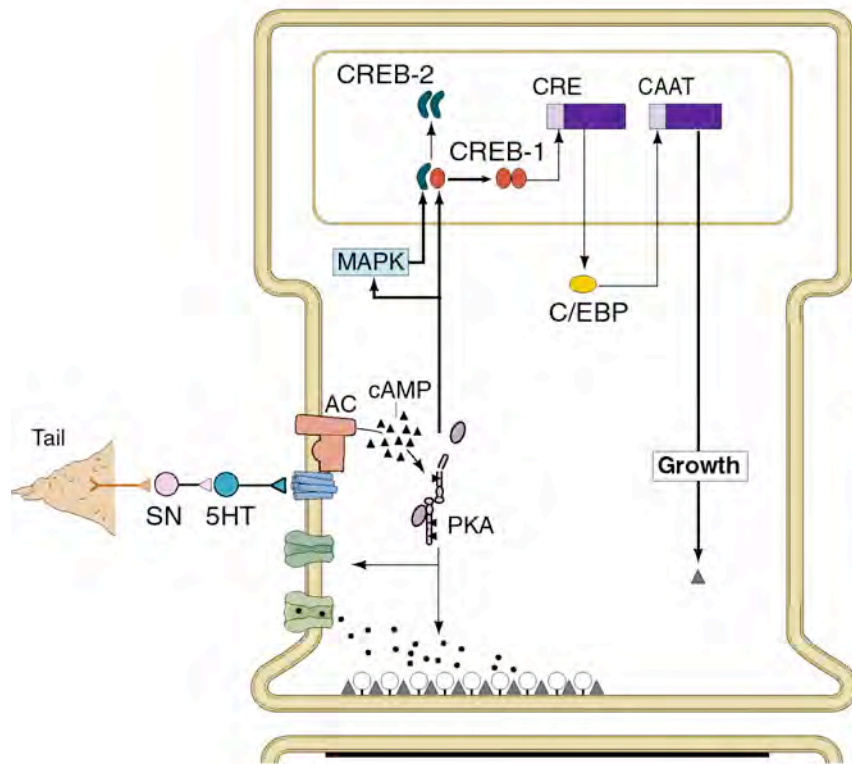


# Dopamine as a Candidate Mediator of Attention

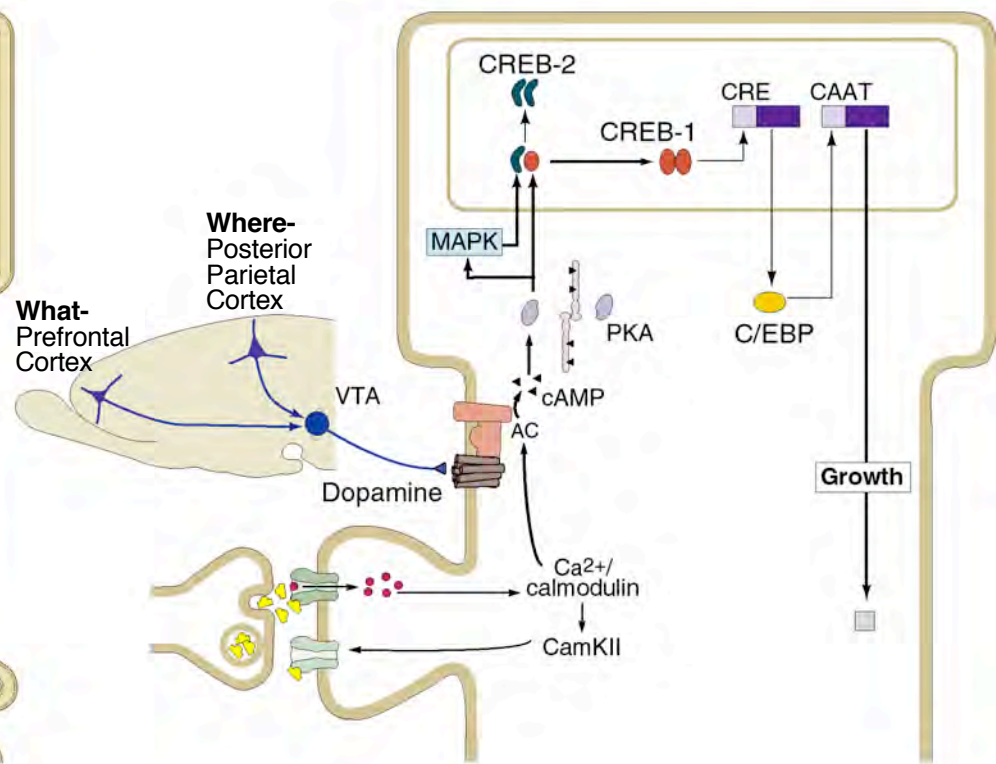


# Both Explicit and Implicit Memory Storage Use Modulatory Transmitters as a Salience Signal and a CREB-Mediated Transcriptional Switch for Converting Short-term to Long-term Memory

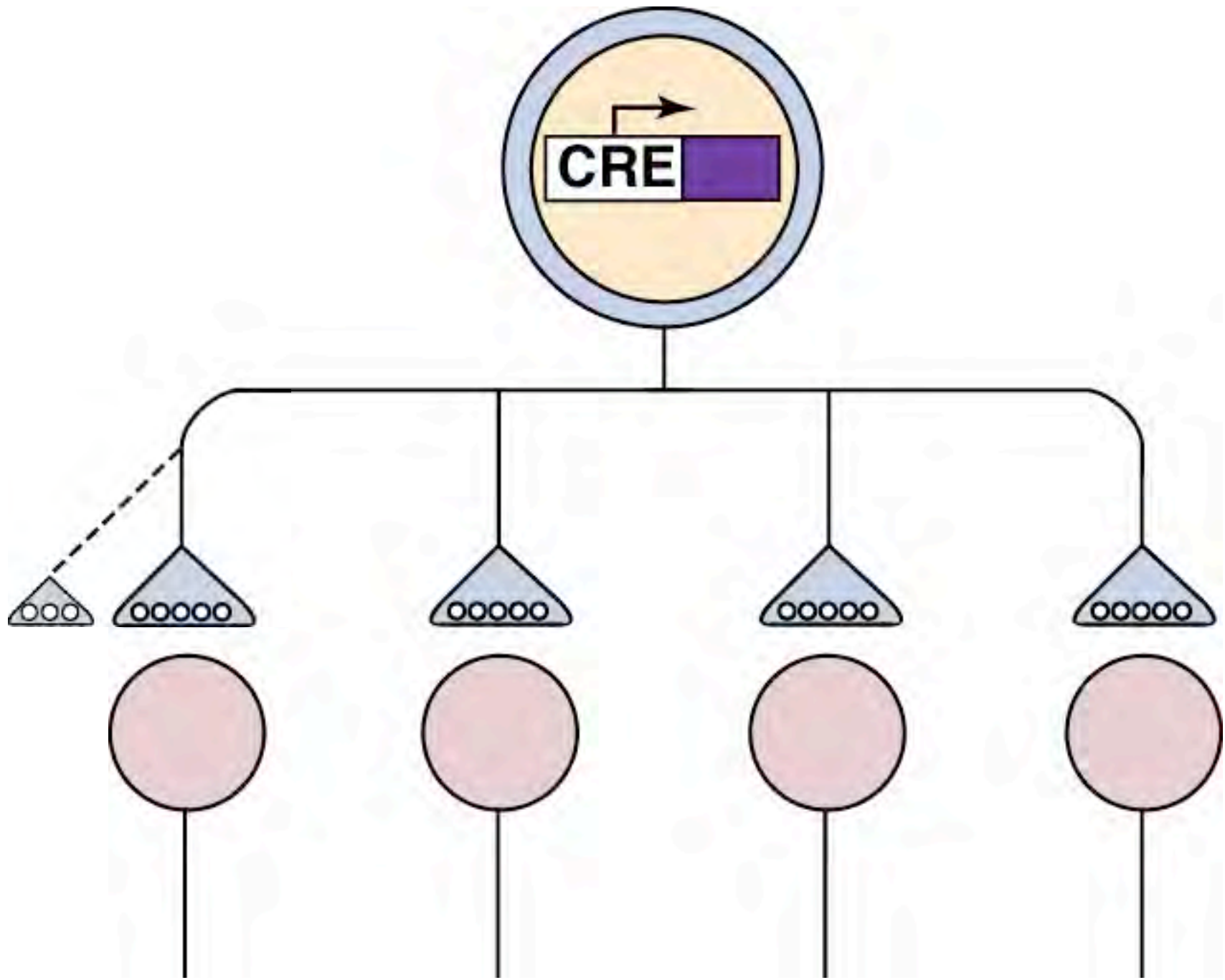
**Aplysia**  
(bottom up modulation)

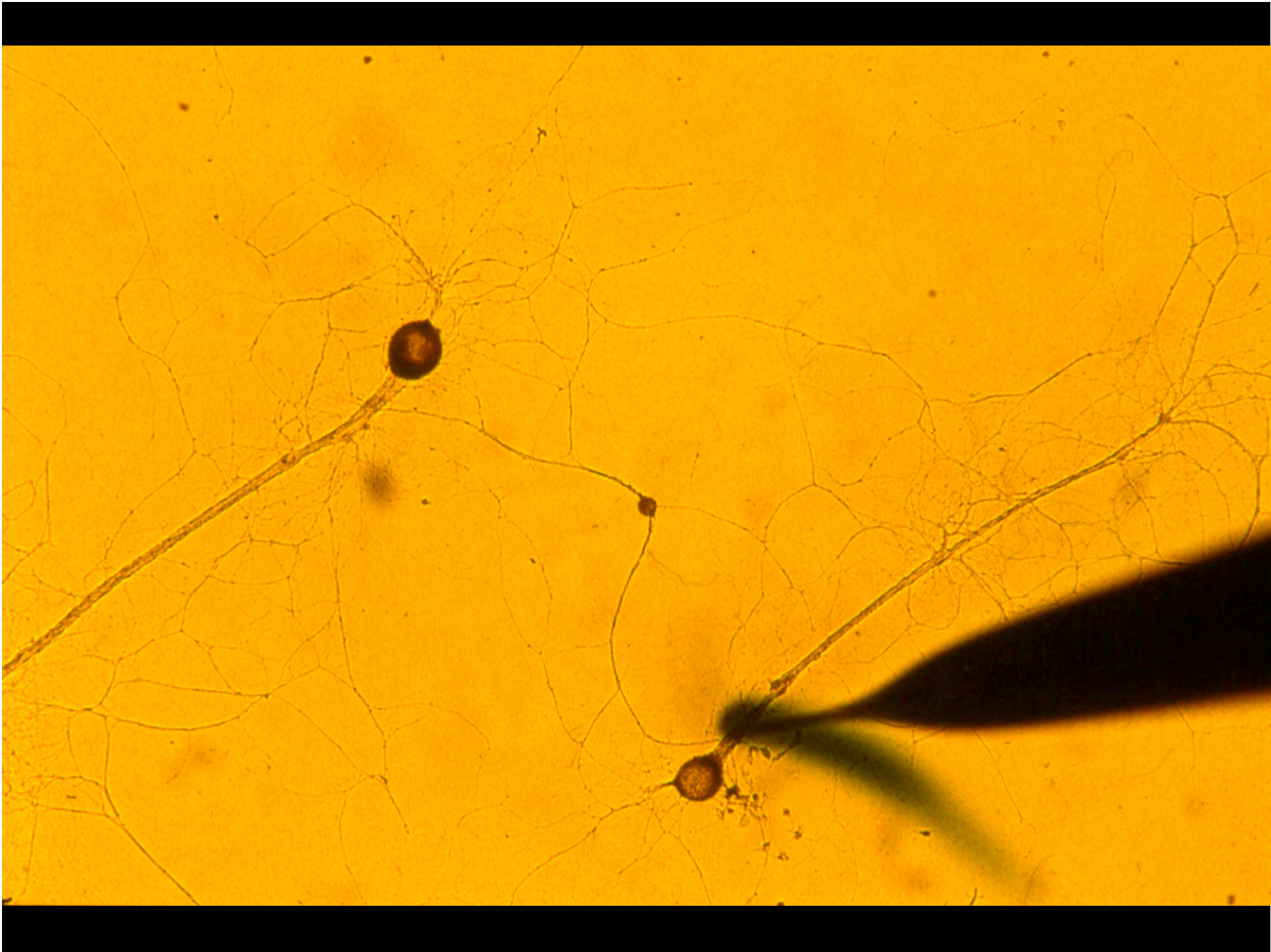


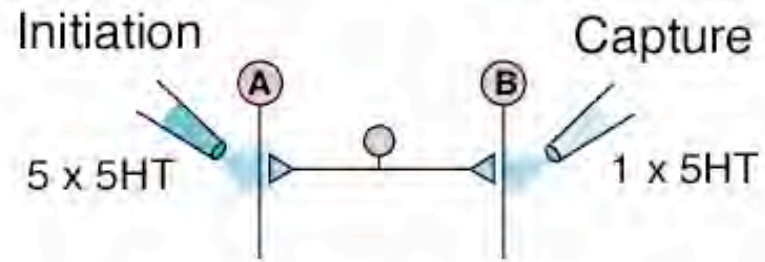
**Hippocampus**  
(top down modulation)



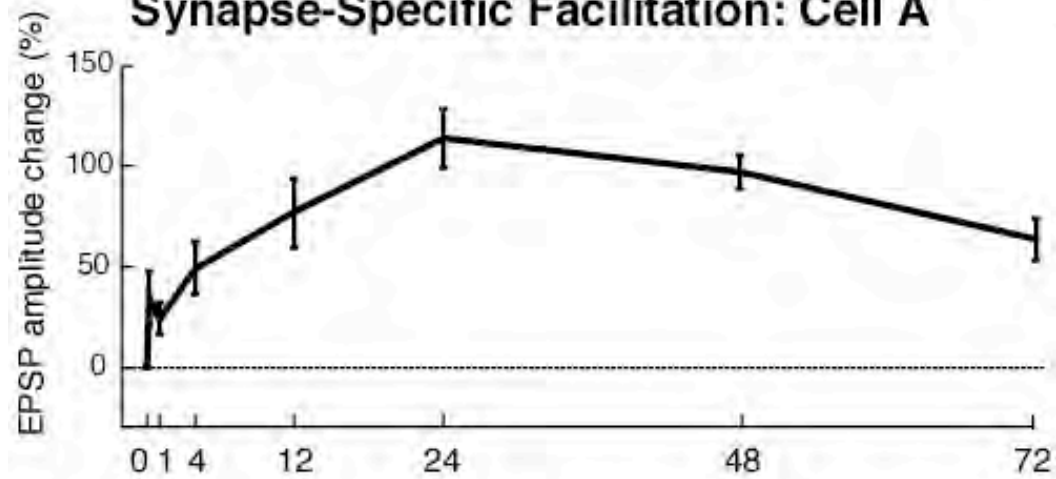
How is synapse specificity achieved? How is it maintained for the long term?



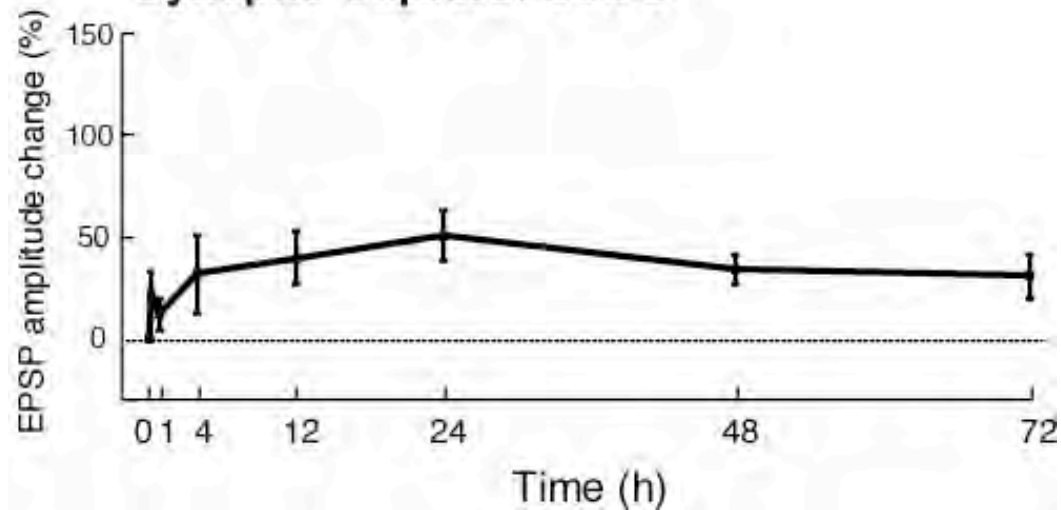




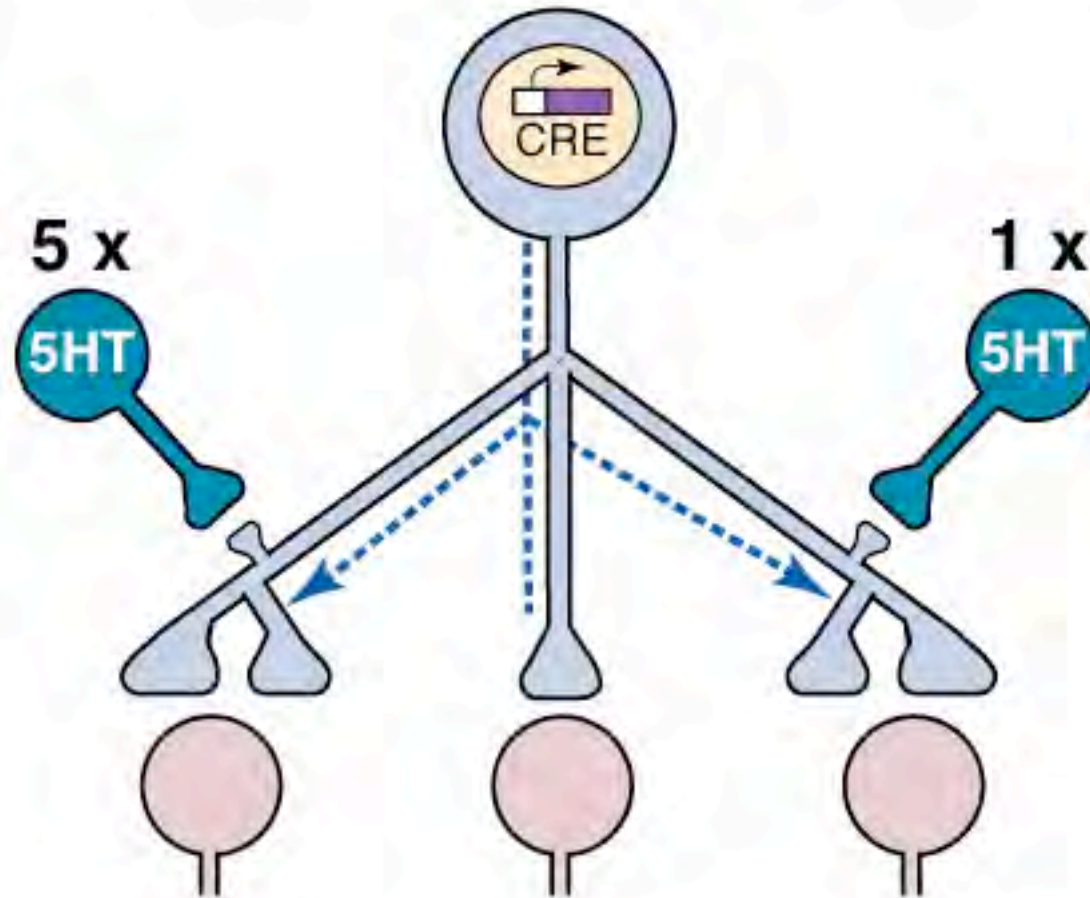
### Synapse-Specific Facilitation: Cell A



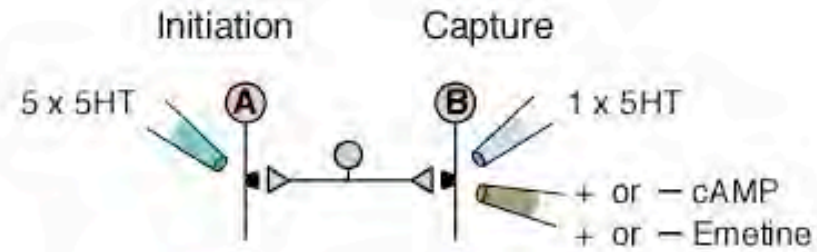
### Synaptic Capture: Cell B



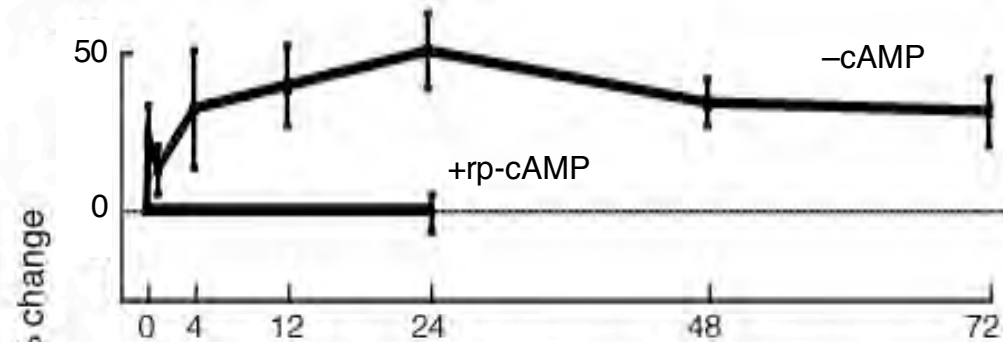
# What is the Molecular Nature of the Synaptic “Mark”?



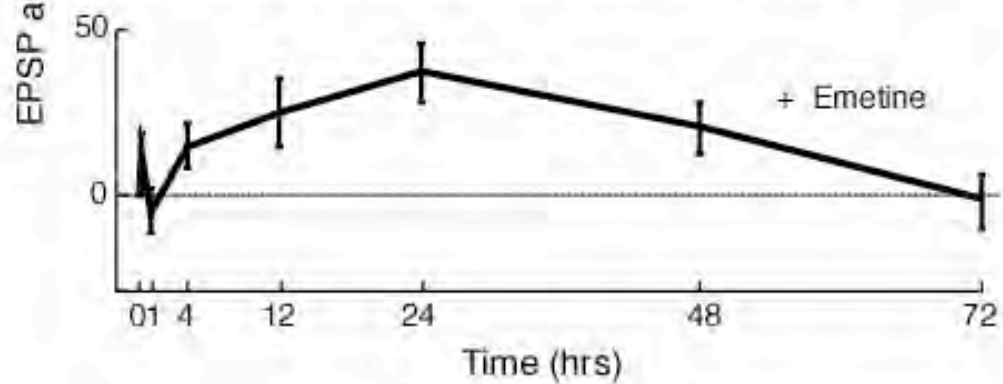
## There are Two Molecular Components to the “Synaptic” Mark



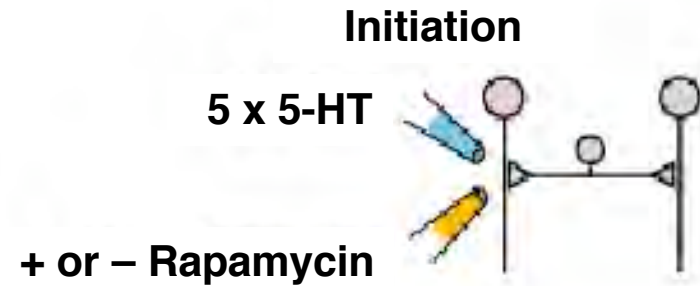
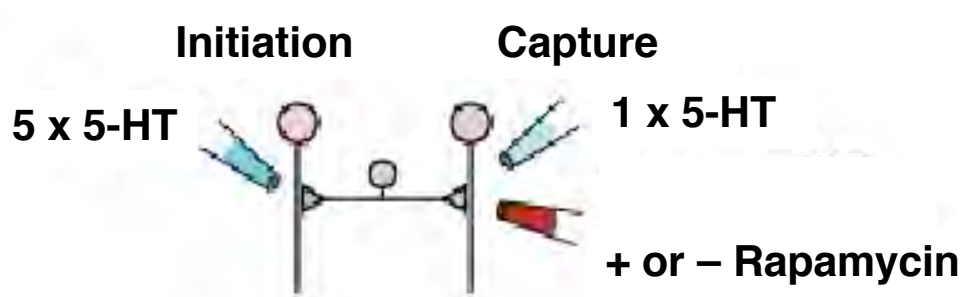
### Synaptic Capture + or - cAMP: Cell B



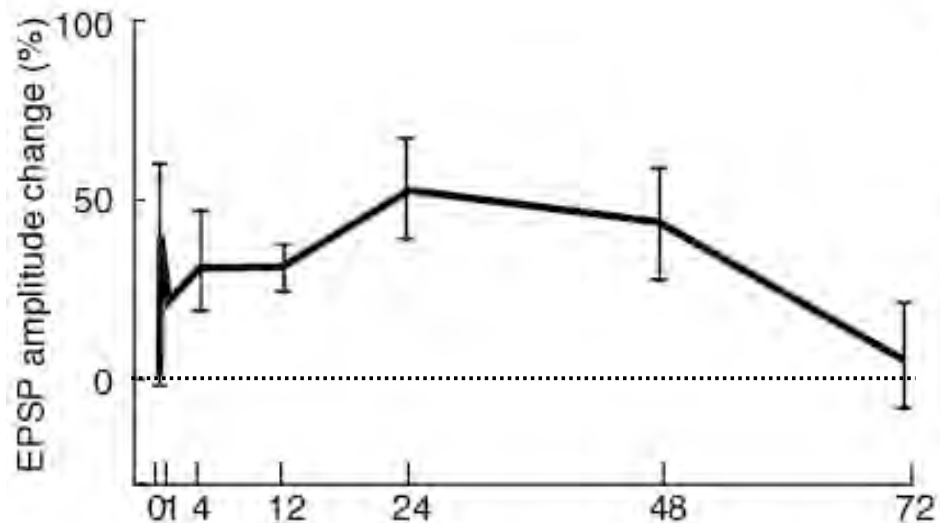
### Synaptic Capture + Emetine: Cell B



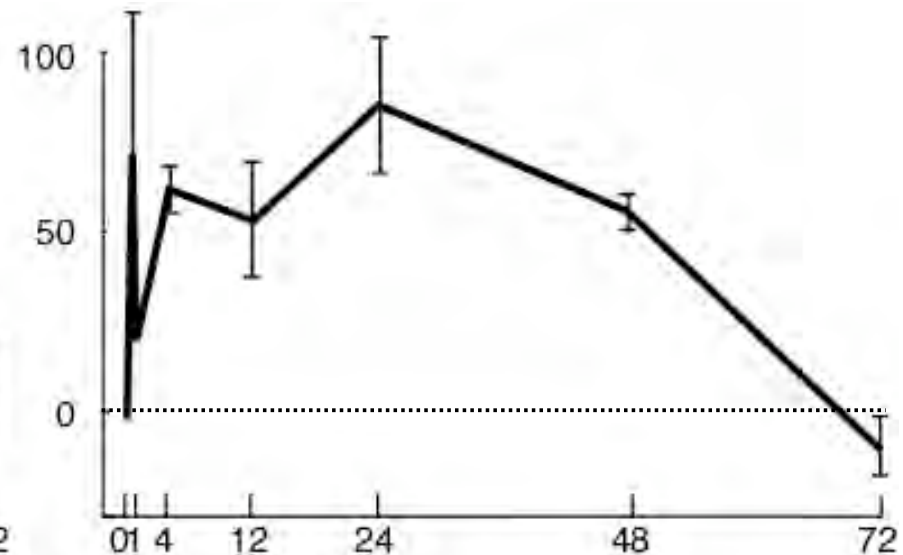
# Rapamycin, a Selective Inhibitor of Protein Synthesis also Blocks the Growth-Dependent Late Phase of LTF



**Synaptic Capture + Rapamycin**

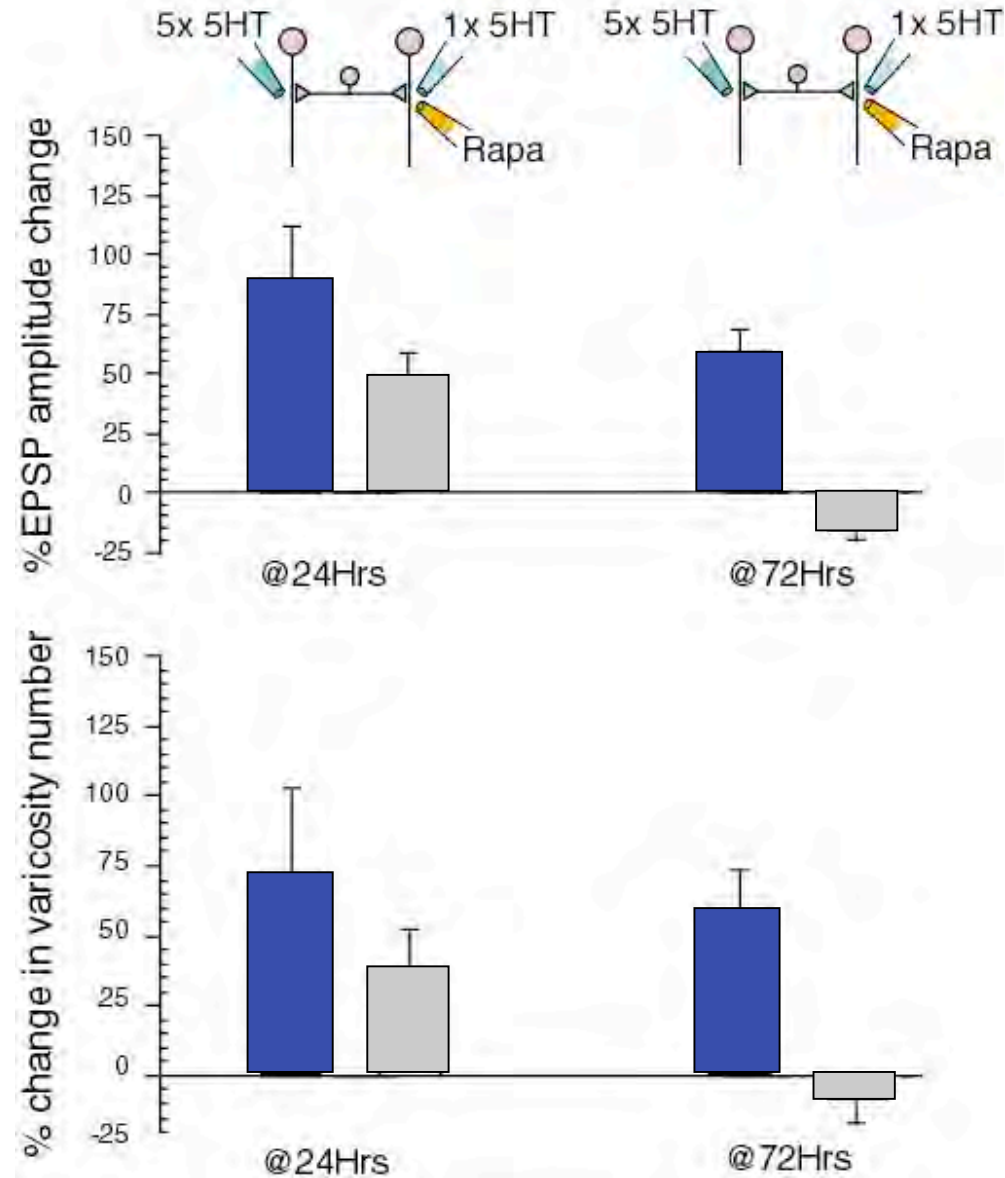


**Synaptic-Specific LTF + Rapamycin**

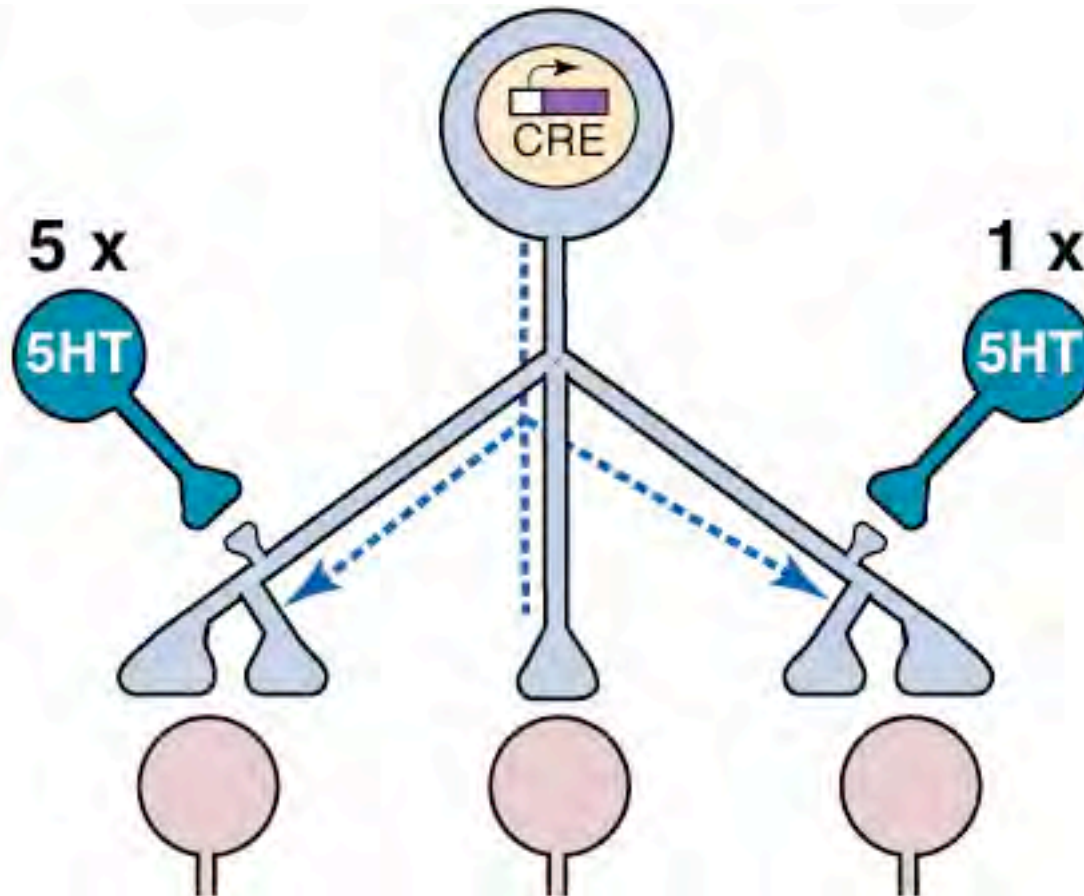


# Rapamycin Blocks the Maintenance of Growth @ 72 Hrs

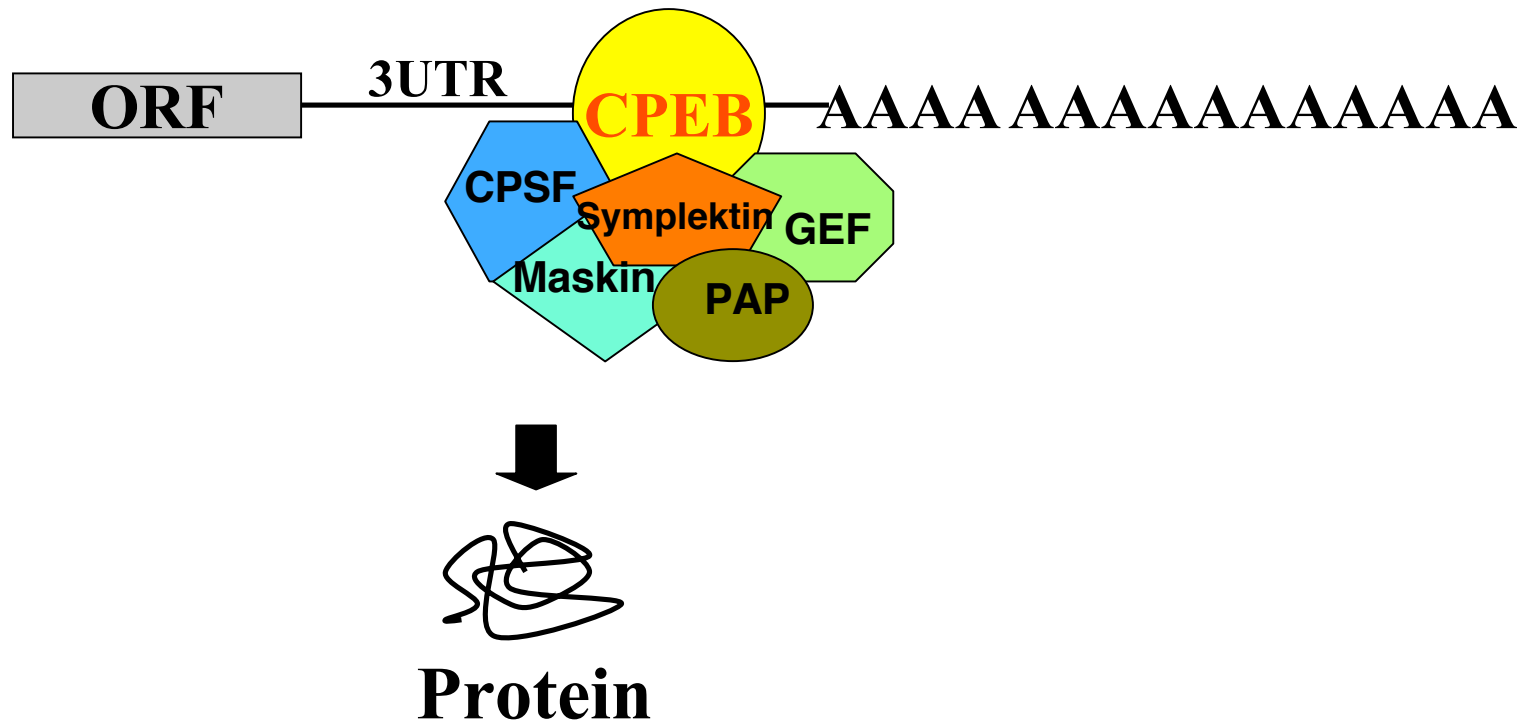
Capture+rapamycin



# What is the Function of Local Protein Synthesis? How are the mRNAs that are Transported to the Synapse Activated Locally?

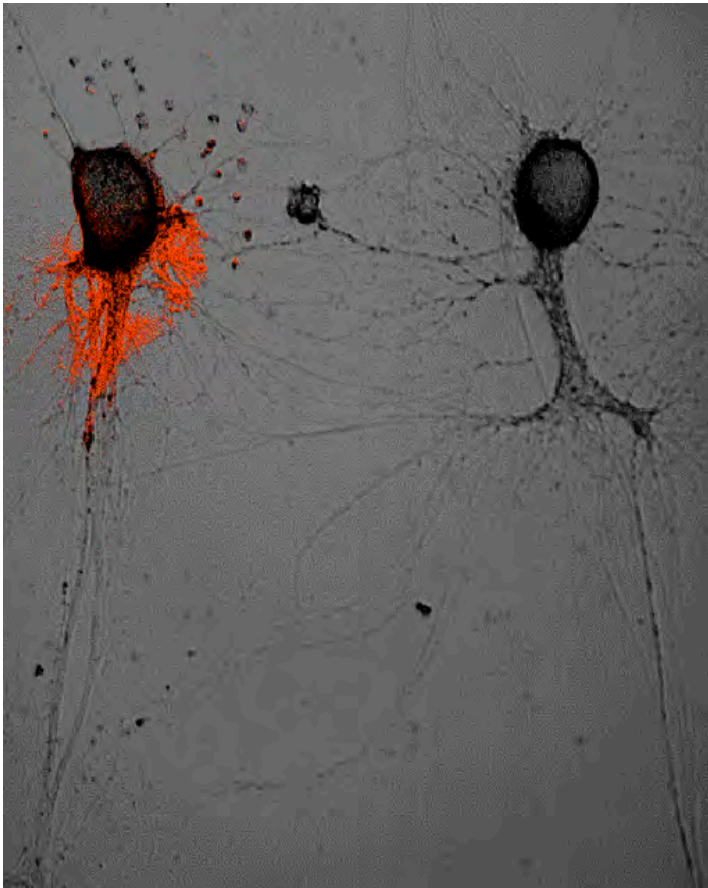


# The **C**ytoplasmic **P**olyadenylation **E**lement **B**inding Protein Can Activate Dormant mRNA

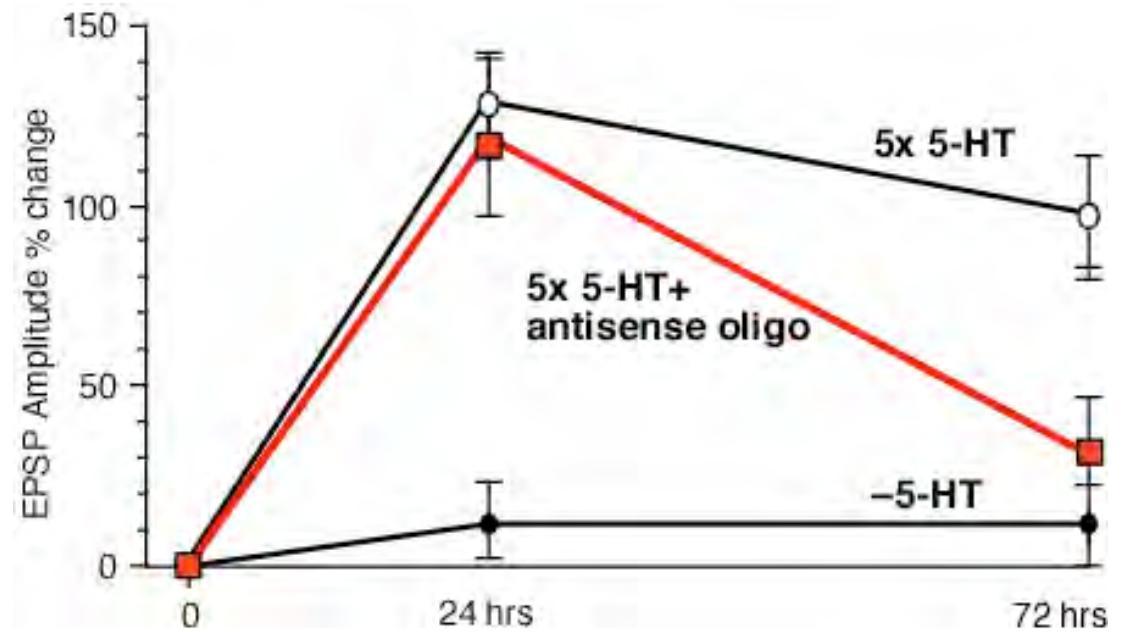


Richter And Colleagues

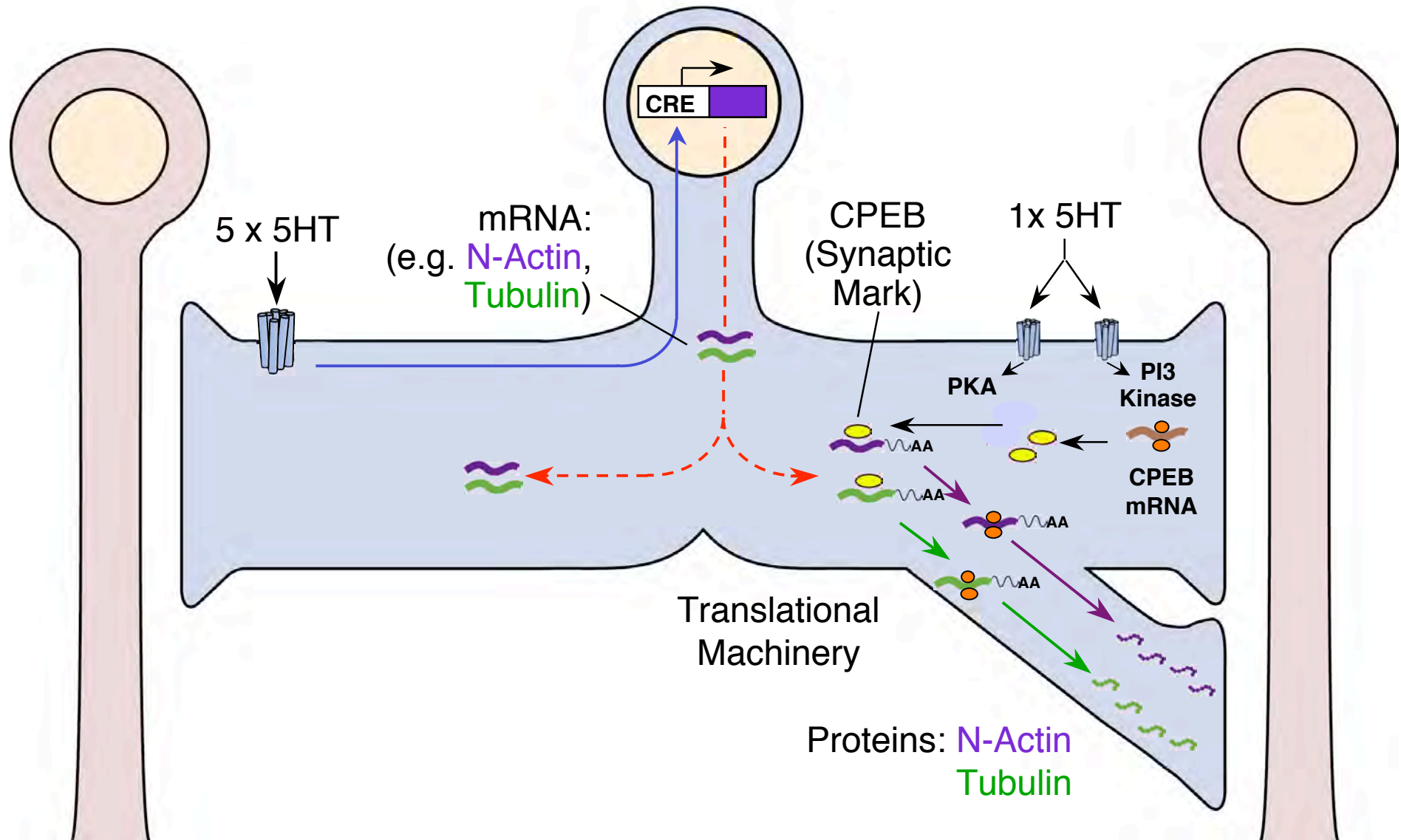
## Branch-specific transduction of tat-ss-CPEBAS1 in L15



## Local inhibition of CPEB blocks maintenance of LTF



# CPEB: A Switch for Activating Local Protein Synthesis

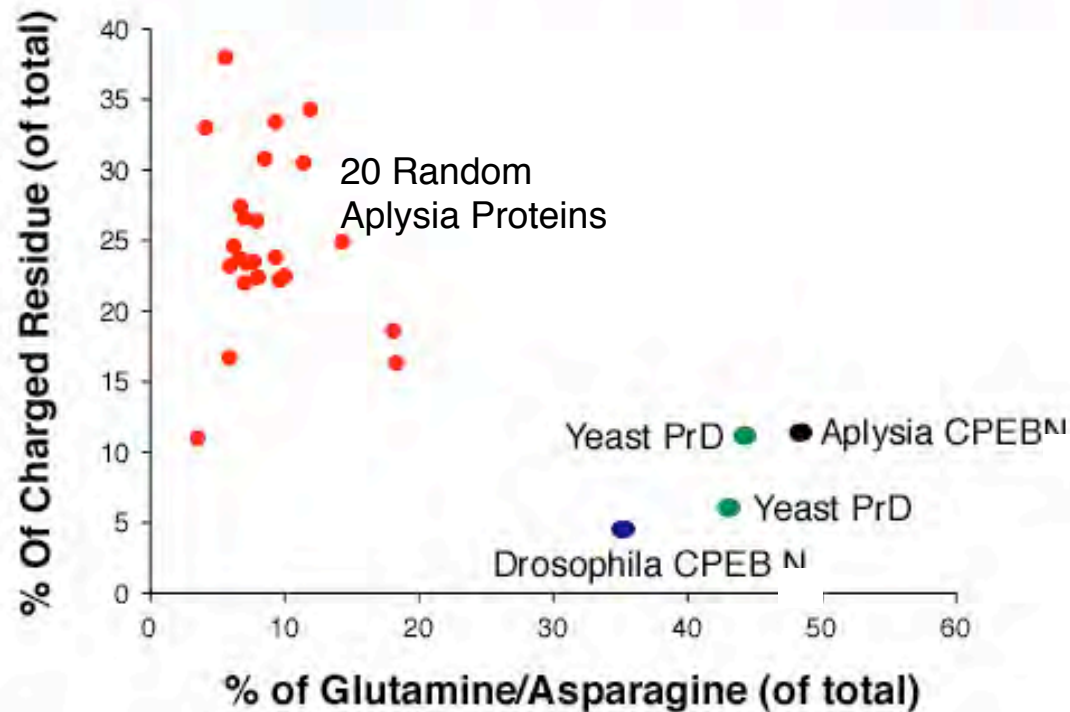


**How does CPEB remain active for the long term  
in the absence of any further synaptic stimulation?**

# A Prion-Like Domain at the N-terminal End of Aplysia CPEB

Aplysia CPEB (1-160)

MQAMAVASQS PQTVDQ<sup>Q</sup>AISV **KTDYEDNQQE** HIPS**NFEIFR**  
**R**INALL**D**NSL **E**ANNVSCS**Q**S **Q**S**Q**Q**Q**Q**Q**Q**T**Q **Q**Q**Q**Q**Q**Q**Q**Q**Q**Q ~48% **Q/N**  
**Q**Q**Q**HL**Q**Q**V**Q**Q** **Q****R**LL**K**Q**Q**Q**Q**Q **A**Q**R**Q**Q**I**Q**Q**Q**L L**Q**Q**Q**Q**K**Q**Q**L  
**Q**Q**Q**Q**Q**Q**E**Q**L**Q **Q**Q**Q**L**Q**L**Q**Q**Q**L **Q**Q**Q**L**Q**HI**Q****K**E PSSHTYTPGP



# Properties of a “Prion”

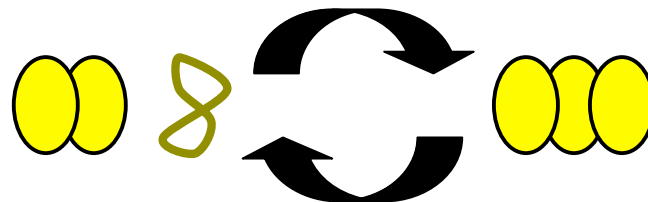
- 1) Two distinct conformational states: one of which forms aggregate.



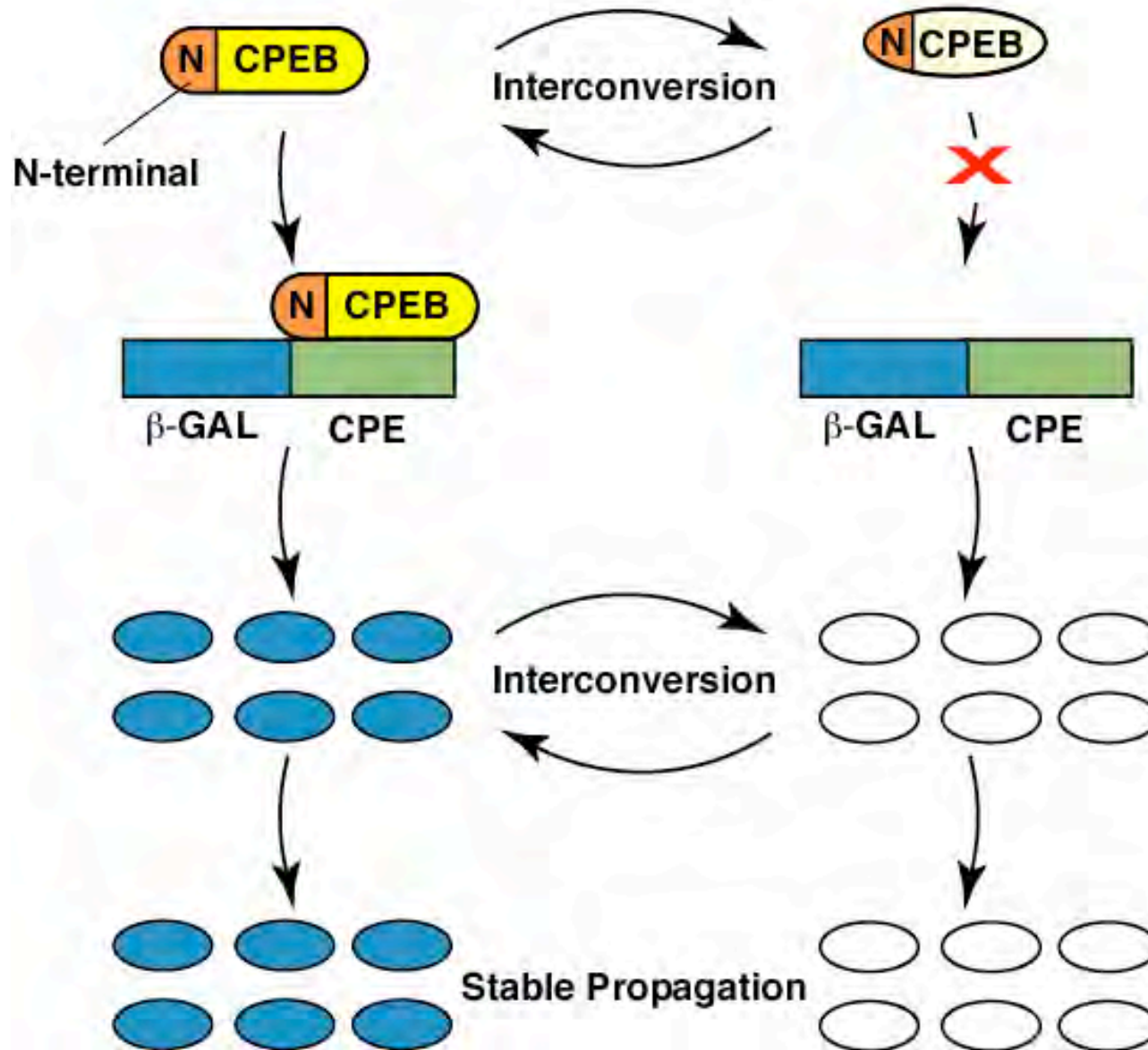
- 2) The conformational states are metastable and functionally distinct

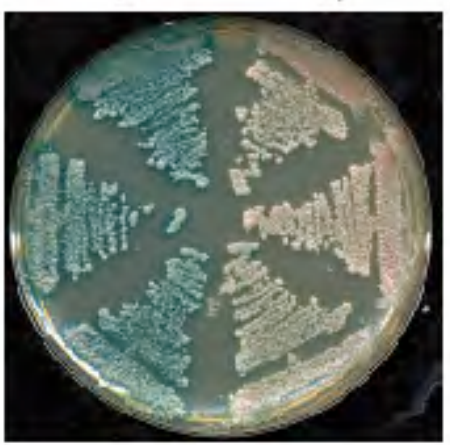
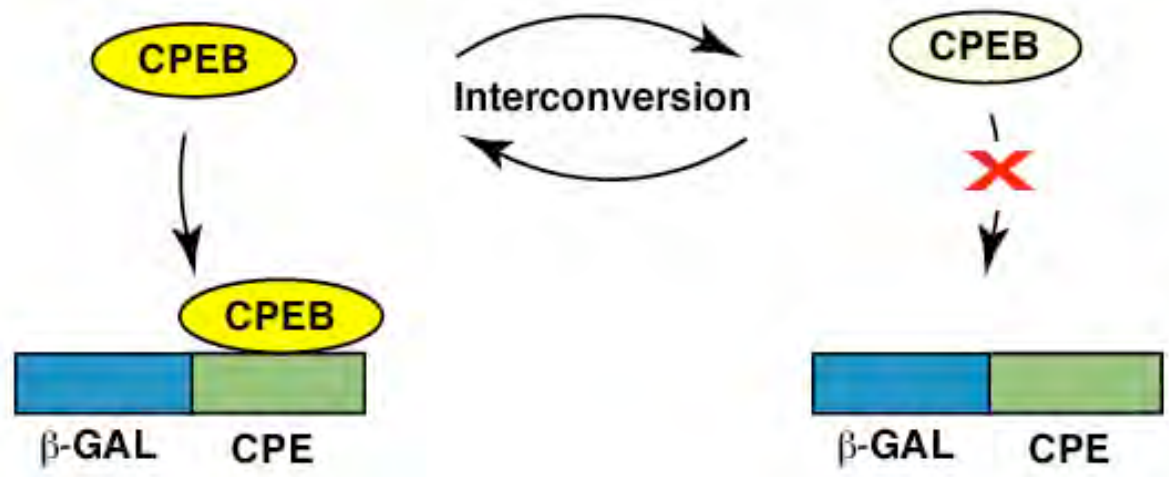


- 3) The aggregated state is self-perpetuating

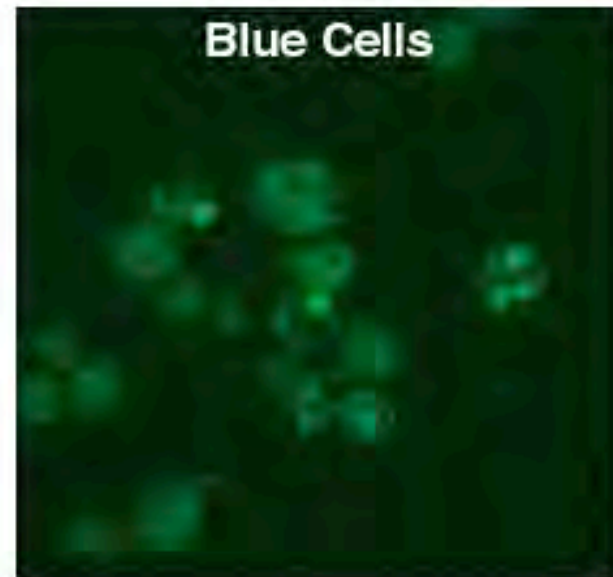
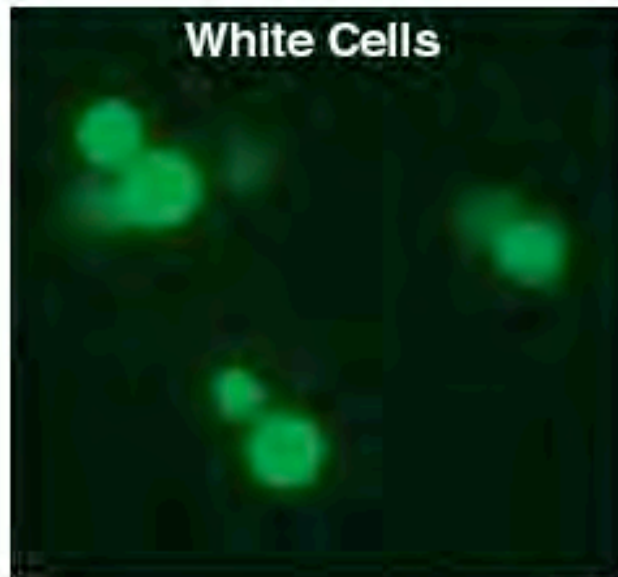
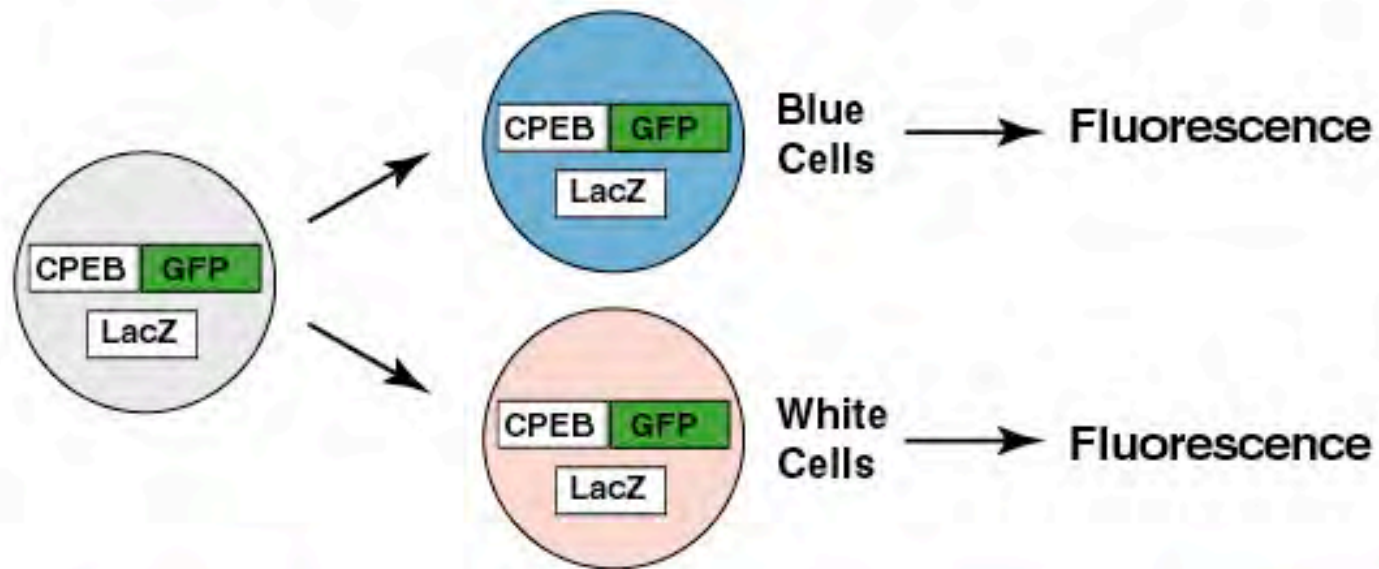


# The Full-Length CPEB Protein Can Exist in Two Functional Conformational States

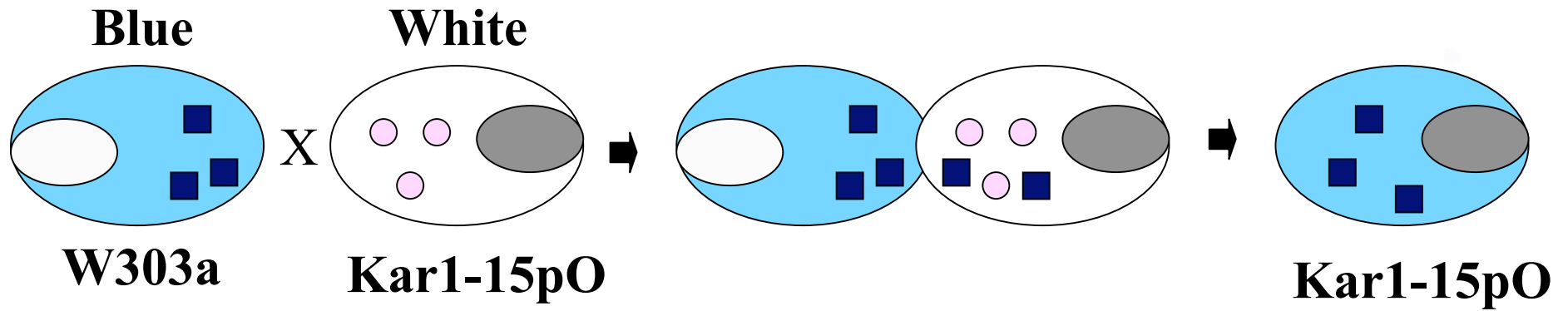




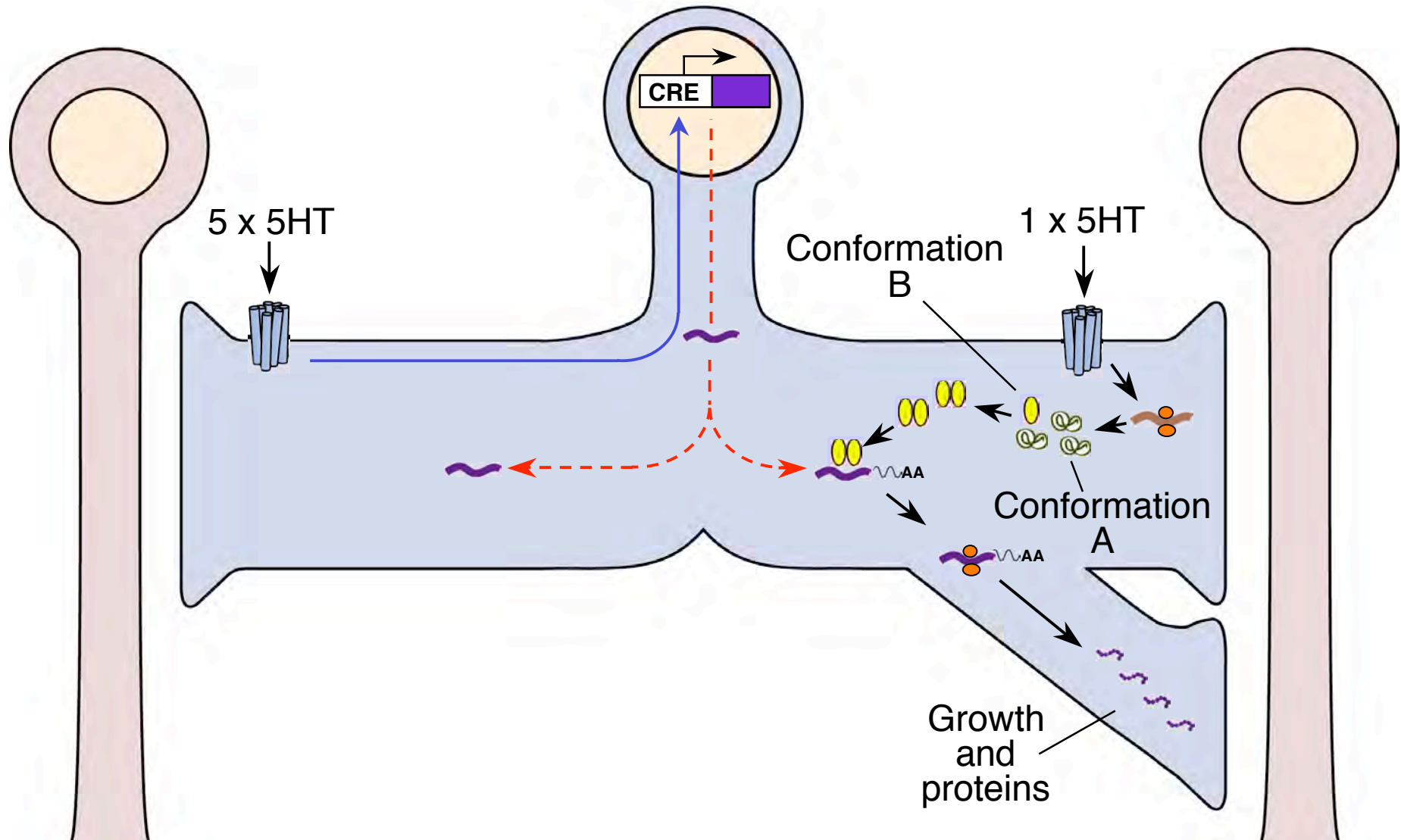
# Aplysia CPEB Forms a Multimeric Structure in Blue Cells



# Dominant Cytoplasmic Inheritance of the Blue state



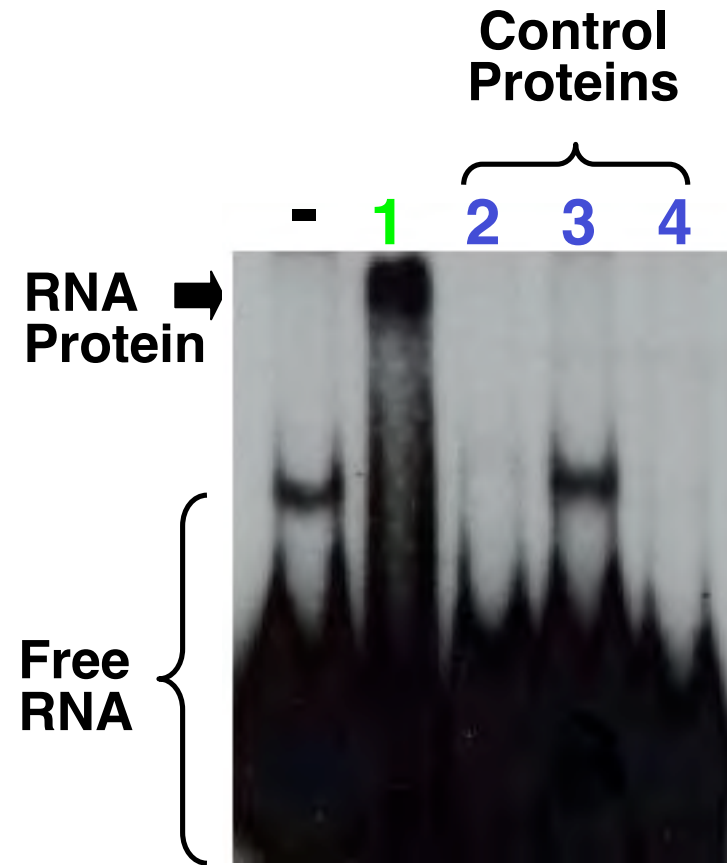
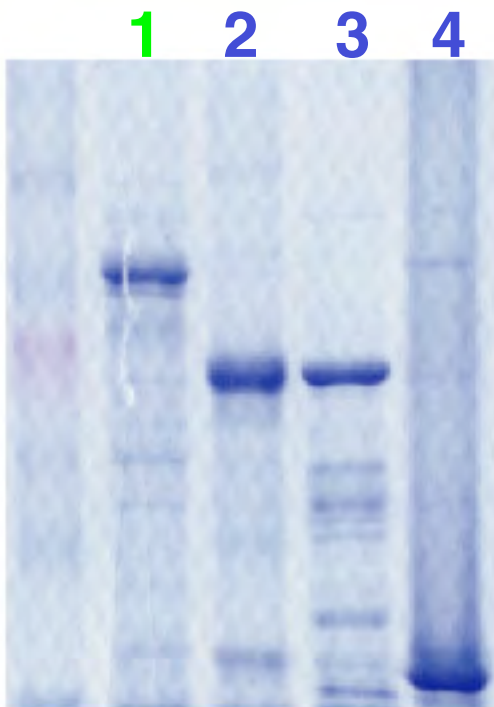
# CPEB as a Candidate for the Self-Perpetuating Switch of Local Protein Synthesis



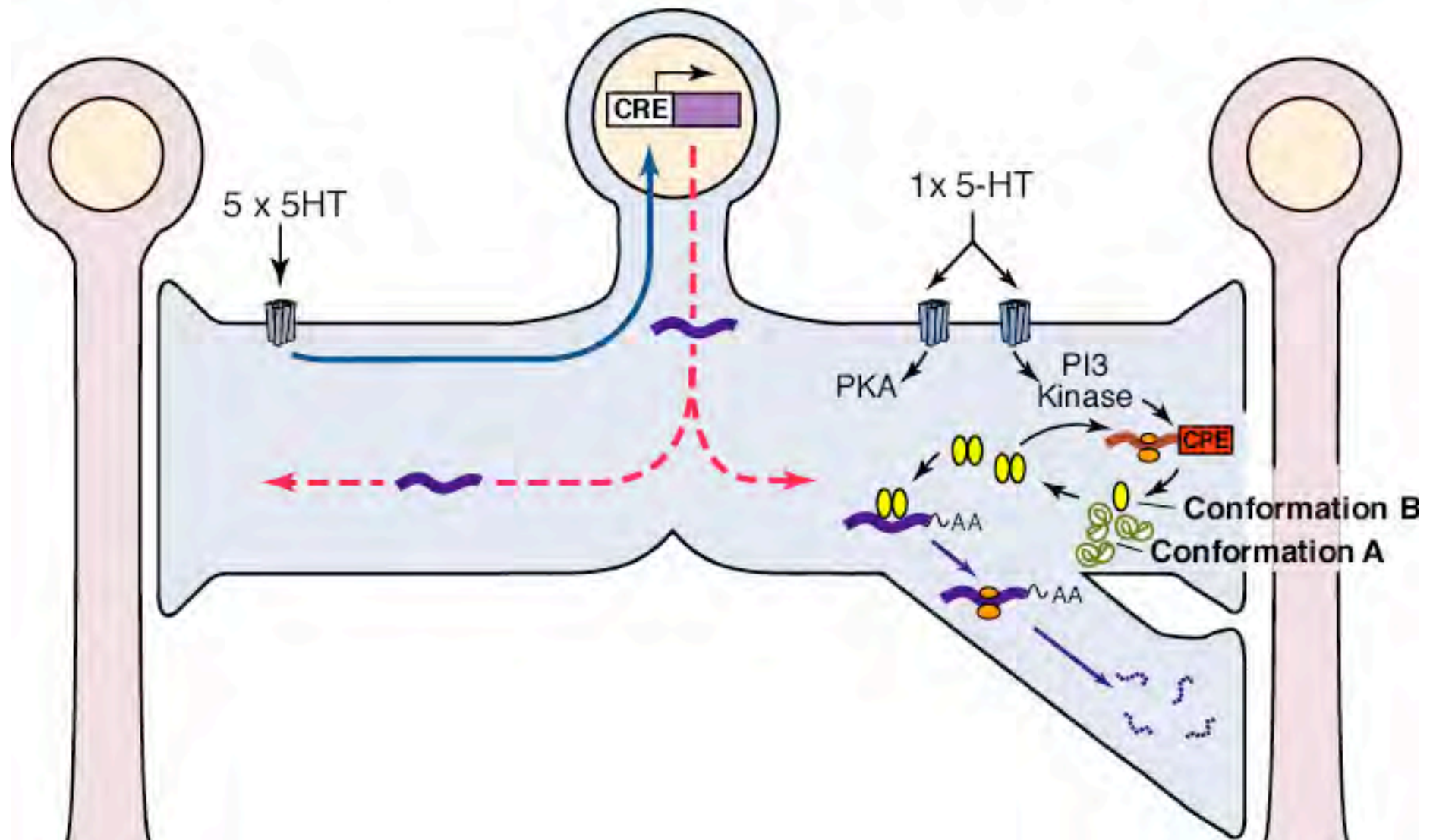
### 3) Is the Aggregated Form The Active Form of CPEB? Only Aggregated *Aplysia* Neuronal CPEB Protein Binds Selectively to CPE-Containing RNA

- 1) *Aplysia* CPEB
- 2) mCPEB1
- 3) GEF
- 4) melF6

Purified proteins

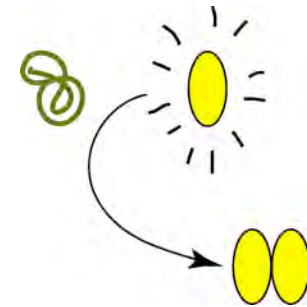
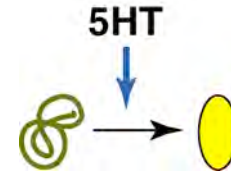


# The CPEB mRNA has a CPE which could Contribute to the Self-Perpetuating Switch for Local Protein Synthesis



# The “Prion-Like” Properties of *Aplysia* CPEB Are Different from Known Prions

- The conversion from one state to the other is regulated by a physiological signal.
- The dominant self-perpetuating state is the active state.

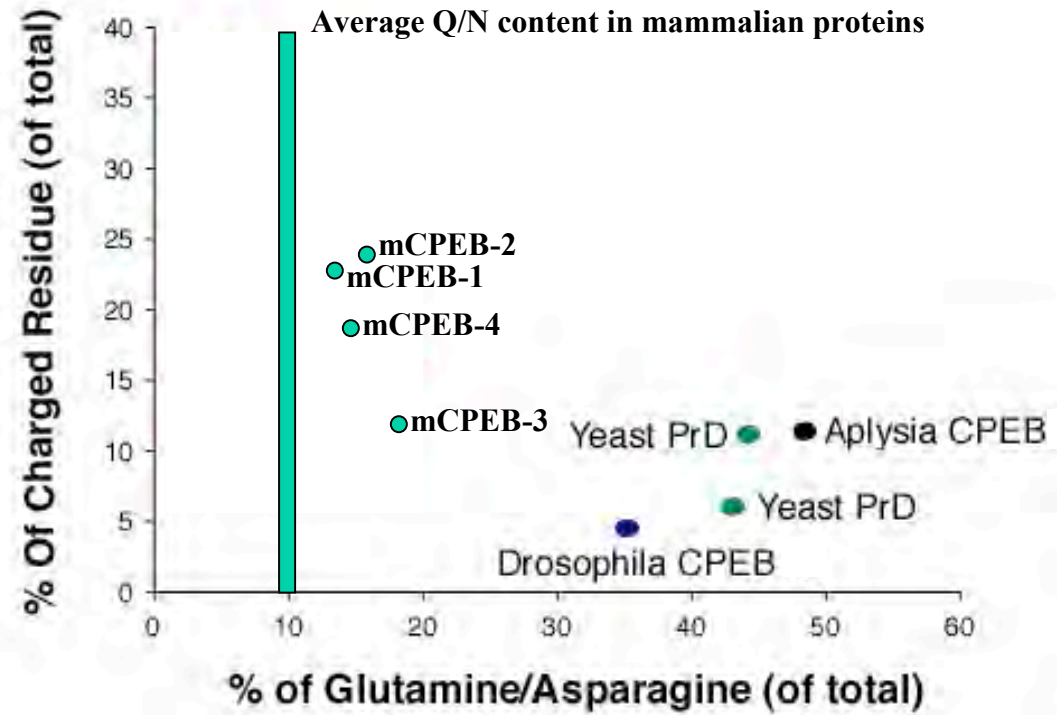


*Aplysia* CPEB might be representative of a new class of proteins with prion-like properties, which has normal physiological function.

# A Prion-Like Domain at the N-terminal End of Mouse CPEB-3: Comparison with *Aplysia* CPEB

**Aplysia CPEB (1-160)** MQAMAVASQSPQTV**DQAISVKT** **DYED** **NQQE** HIPS**NFEIFRR** INALL**DNSL**  
**EANNV** SCSSQSQS**QQQQQQ** T**QQQQQQQQQQQQQQQQ** HL**QQVQQQRLLK** ~48% Q/N  
 QQQQA**QR** QQI**QQ** LL**QQQQQK** QL**QQQQQQE** QL**QQQQ** LQL**QQQL**  
 QQQL**QH** IQ**KE** PSSHTYTPGP

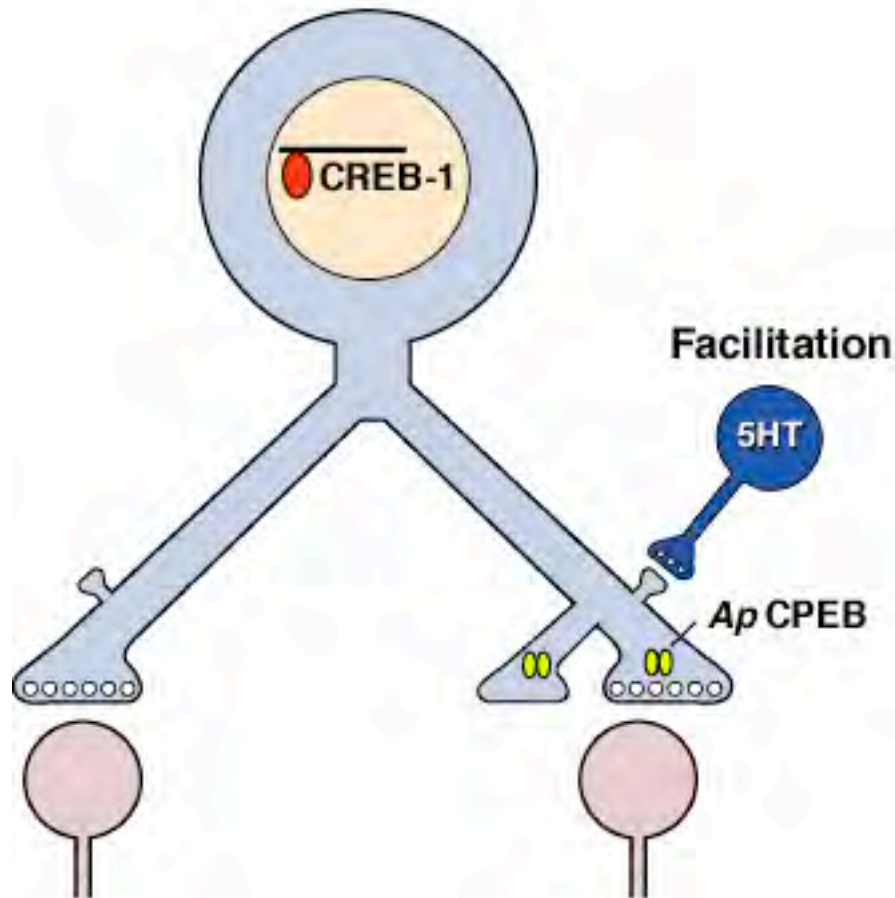
**mCPEB-3 (1-232)** **MQDDLLMDKSK** TQPQS**QQQQR** **QQQQQQQQ** QL**QPE** PGAA**E** APSTPLS**SEIP**  
**KPED** SSAVPALSPASAPPAP**NGPDKM** Q**ME** SPLLPGLSFH**QPPQQ** P**PP** **QEPT** ~18% Q/N  
 APGASLSPSFGSTWSTGTT**NAVED** SFF**Q** GITPV**NGT** MLF**Q** NFP**HHV** NPVFGG  
 TFSP**Q** IGLA**QT** Q**HH** **QQ** P**PP** P**AP** **QPP** **QPA** **QPP** **QA** **QPS** **QQRR** SPASPS**Q** APYA**Q**  
 RSAAAYGH**Q** PIMTS**K** PSSSSAVAAAAA



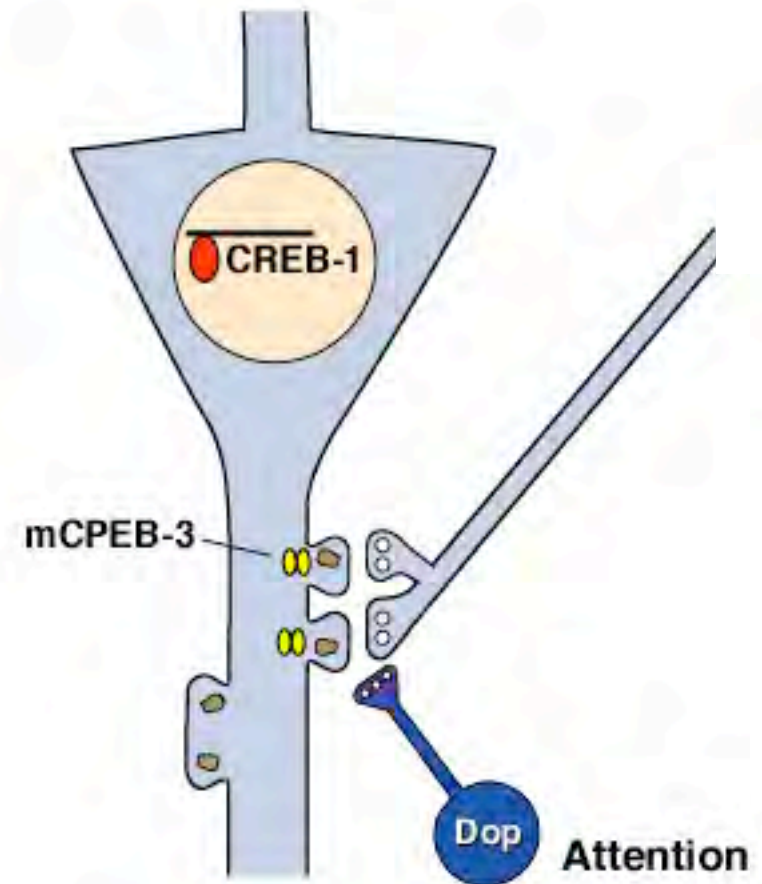
# Modulatory Transmitters Serve as Salience Signals to Stabilize Synaptic Plasticity and Behavior for Both Implicit and Explicit Memory

Is the mechanism for maintenance also general?

Implicit Memory:  
Sensitization in Aplysia



Explicit Memory:  
Spatial Memory in the Mouse



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