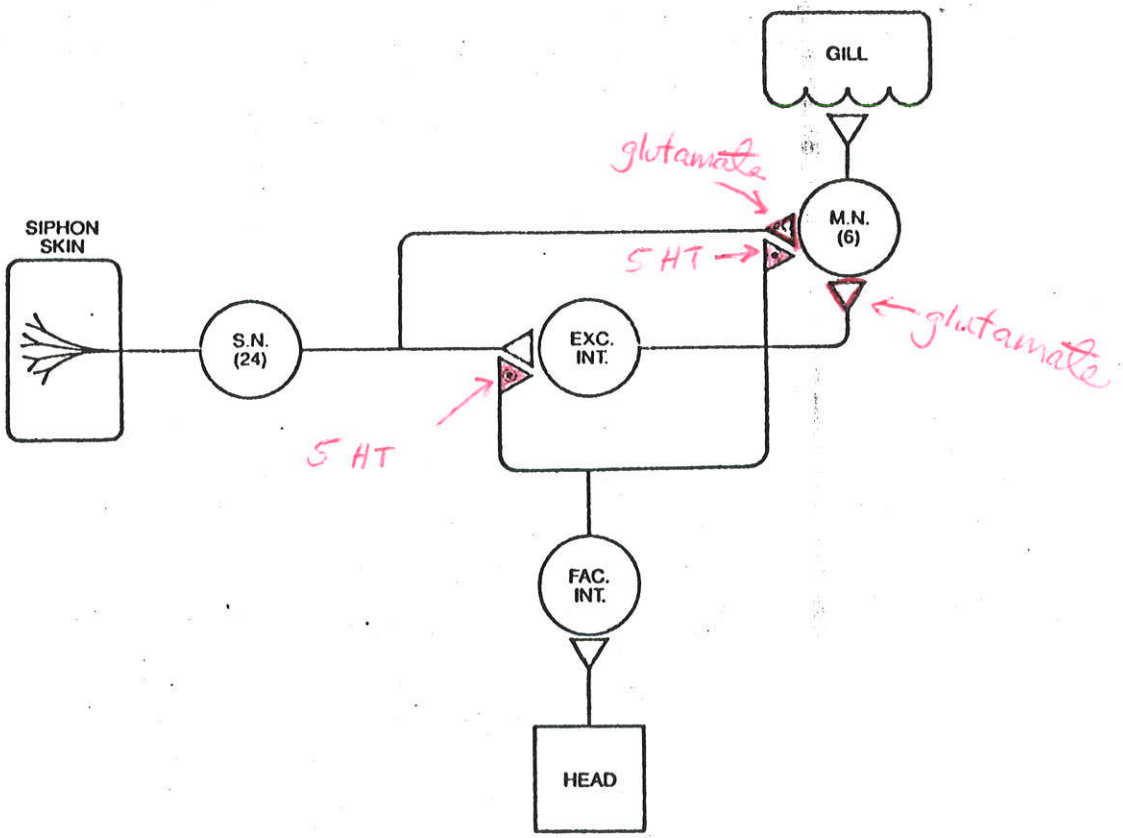
Schematic of neural network of Aplysia (underlying learning + memory)



Habituation
Sensitization
Conditioning

9.03 Neural Basis of Learning and Memory: Lecture 3

Sensitization and Conditioning in Aplysia: Cellular mechansisms

- *Sensitization (pseudoconditioning)* - Enhancement of response to a variety of stimuli following stimulus exposure.

- In Aplysia, head or tail stimulation enhance the gill withdrawal response to siphon stimulation
- The mechanism of sensitization of this response is the heterosynaptic facilitation of presynaptic transmission.
- Both short and long term forms can be elicited dependent on activity levels

Segue to the basic principles of second messenger processes

- Synaptic transmission can be mediated either directly through ligand gated channels or indirectly through second messenger systems.
- Synaptically activated second messengers act through G protein coupled receptors. (Ligand binds to the receptor and activates the G protein which activates a primary effector, which produces the second messenger, which is typically diffusible).
- The process can be summarized as:

  receptor ->G protein -> primary effector -> second messenger -> secondary effector

- Examples of second messengers are cyclic adenosine monophosphase (cAMP), inositol triphosphase (IP3), diacylglycerol (DAG), arachidonic acid.

  Examples of primary effectors are adenylyl cyclase producing cAMP, phospholipase C (PLC) producing IP3 and DAG, and phospholipase A (PLA) activating arachidonic acid. Either the G protein or the second messenger then act on a channel to modify ionic across the cell membrane.

  Protein kinases

- The second messenger can also activate a secondary effector, such as a protein kinase, which acts on the channel. For example cAMP activating the cAMP dependent protein kinase, or DAG activating protein kinase C (PKC).
- second messangers can act through kinases which phosphorylate proteins. The addition of a phosphate group to a channel protein can provide the energy needed for opening or closing. The kinase can also phosphorylate regulatory proteins which then act on the channel.
- Kinases have regulatory and catalytic subunits.
- Exposure or cleavage of the catalytic subunits frees them to phosphorylate proteins.
-

Back to sensitization

- The process of facilitation involves activation of seretonergic inputs from facilitating interneurons which are stimulated by sensory input.
- This activates the cAMP second messenger system ->

- seretonin binding to the 5-HT receptor activating a G protein

- G protein activates adenylyl cyclase

- Adenylyl cyclase increases the activity of cyclic AMP

- cyclic AMP activates a cAMP dependent protein kinase

- The short-term facilitation is produced by the phosphorylation of a K+ channel which causes it to close, decreasing potassium current out of the cell, increasing excitability and prolonging Ca++ influx during action potentials.
- Availability of transmitter is also enhanced by the action of cAMP dependent protein kinase and that of protein kinase C (PKC) which is activated by the PLC->DAG second messenger system.

Long-term facilitation acts through the same cAMP signalling system.

Second messengers can induce new protein synthesis by regulating gene expression.

Segue to gene regulation

- Genes are typically made up of two regions. The *regulatory* region and the *coding* region. Regulatory regions are additionally subdivided into *enhancer* and *promoter* regions. Activation of the coding region, which contains the information for transcription, is regulated by the binding of regulatory proteins to the enhancer region. The portions of the enhancer region which bind specific regulatory proteins are known as *response elements*. An example of this is the cyclic AMP response element (CRE) which recognizes cyclic AMP response element binding (CREB) proteins.

Back to sensitization

- With increasing levels of cAMP production, PKA is activated. PKA can translocate to the nucleus where it phosphorylates CREB proteins which bind to the CRE regions of genes which encode certain proteins which may produce long-term changes in synaptic structure and response through cleavage of the regulatory sub-unit of the protein kinase A, leaving the catalytic sub-unit free to persistently phosphorylate K+ channel proteins, and new growth.

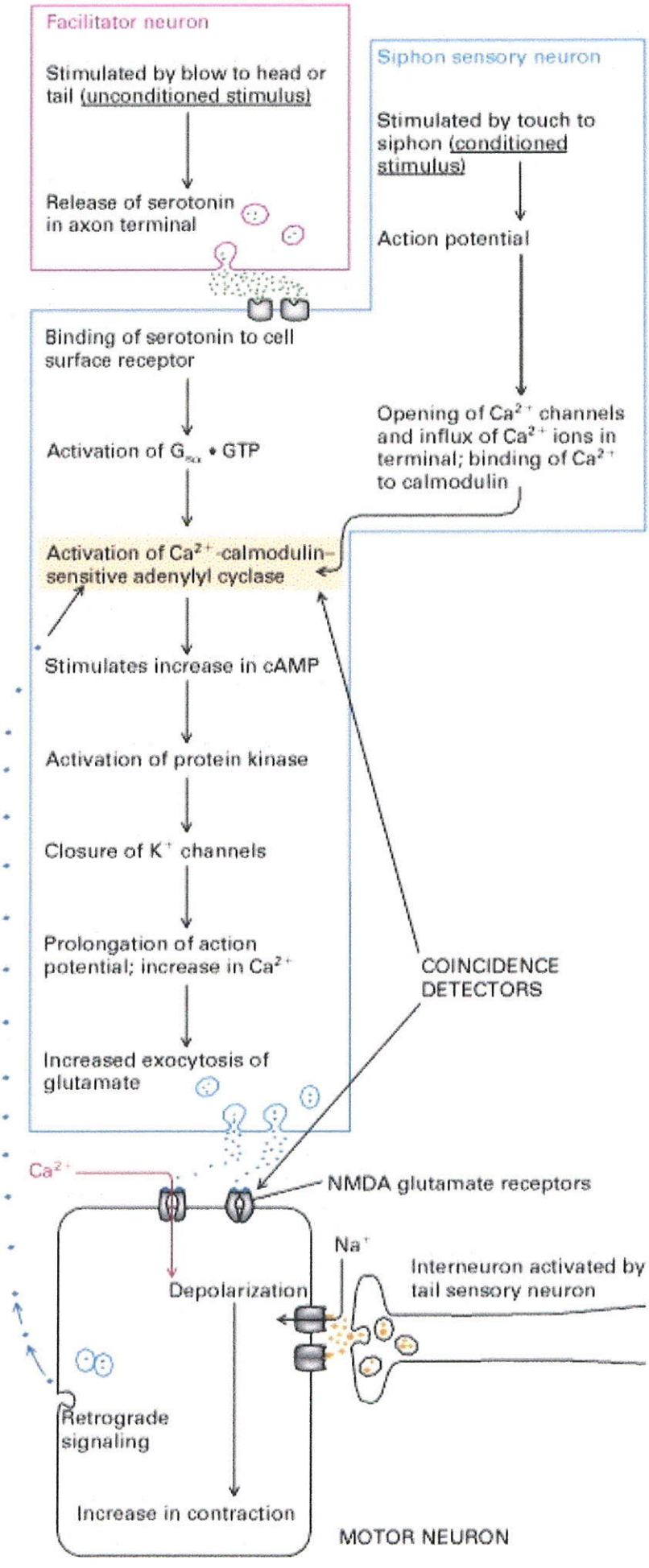
Classical conditioning of gill withdrawal

Related mechansisms are involved in the classical conditioning of the withdrawal response.

The unconditioned stimulus (US) of tail shock produces the UCR of gill withdrawal.

Preceding the tail shock with stimulation of another sensory input (mantle shelf) facilitates the response to mantle stimulation.

The mechanism involves the increase of seretonin activited adenylyl cyclase activity (triggered by tail shock) in the presence of Calmodulin. Calmodulin is dependent on Ca++ which results from activation of Ca++ channels by sensory stimulation (mantle).


Facilitator neuron
Stimulated by blow to head or tail (unconditioned stimulus)
Release of serotonin in axon terminal
Siphon sensory neuron
Stimulated by touch to siphon (conditioned stimulus)
Action potential
Binding of serotonin to cell surface receptor
Opening of Ca^{2+} channels and influx of Ca^{2+} ions in terminal; binding of Ca^{2+} to calmodulin
Activation of $G_{s\alpha}$ • GTP
Activation of Ca^{2+}-calmodulin–sensitive adenylyl cyclase
Stimulates increase in cAMP
Activation of protein kinase
Closure of K^+ channels
Prolongation of action potential; increase in Ca^{2+}
Increased exocytosis of glutamate
COINCIDENCE DETECTORS
Ca^{2+}
NMDA glutamate receptors
Na^+
Interneuron activated by tail sensory neuron
Depolarization
Retrograde signaling
Increase in contraction
MOTOR NEURON