

Lecture 41 – Learning II – Kandel

The CNS of the slug, *Aplysia*, contains far fewer neurons than the mammalian CNS, and many of these are readily identifiable. Thus, it has been a good preparation in which to identify the modifications in synaptic transmission that contribute to learning and the molecular changes that produce these modifications. These molecular mechanisms function in mammalian learning also.

Habituation is a type of implicit learning in which the animal learns to ignore unimportant stimuli. *Aplysia* shows habituation of its defensive gill withdrawal reflex. This is caused by a decrease in the amount of transmitter released from the cutaneous sensory neuron onto the gill motor neuron.

Sensitization is a type of implicit learning in which the animal learns to attend to meaningful (e.g. noxious) stimuli. Here, the release of transmitter from the sensory neuron is increased because of the release of transmitter from a facilitatory neuron onto the sensory synaptic terminals. This transmitter, serotonin, causes a rise in **cAMP** in the sensory terminals. The consequent phosphorylation of target proteins (e.g. ion channels) by activated PKA enhances transmitter release.

Repeated, spaced administration of stimuli produces a long-term (\geq hours), rather than a short-term (~minutes), learning (and underlying synaptic modification). Unlike short-term learning, long-term learning depends on protein synthesis. In *Aplysia* sensitization, the repeated stimuli amplify and prolong the increase in cAMP, spreading the signal intracellularly and permitting catalytic subunits of PKA to diffuse into the SN nucleus. There, along with activated MAP kinase, they affect gene transcription by increasing the activity of the **CREB-1** activator protein and decreasing the activity of the CREB-2 repressor protein. Unlike short-term learning, long-term learning can involve growth or removal of synapses and axonal branches.

Explicit (declarative) learning has best been studied in the mouse, where genetic engineering is a powerful experimental tool. The hippocampus is required for explicit learning. Long-term potentiation (LTP), where a train of stimuli results in increased synaptic potentials in response to subsequent individual stimuli, may be a cellular mechanism for learning. LTP requires the opening of postsynaptic NMDA channels, which permits influx of Ca^{++} . Repeated trains of stimuli cause Ca^{++} to activate adenylate cyclase, raising cAMP levels postsynaptically. This results in LTP which is long-lasting (L-LTP) and depends on protein synthesis. Mouse mutants in which PKA is inhibited specifically in the hippocampus show reduced L-LTP and deficits in explicit, but not implicit, learning.

Experience can alter maps in the cerebral cortex. If a monkey is trained to press a lever repeatedly with certain fingers, the representation of those fingers in the primary somatosensory cortex expands. Persons who started training as violinists before puberty show an expansion of the representation in the primary motor cortex of the fingering, but not the bowing, hand. These changes in maps suggest underlying alterations of neuritic arbors.

Summary

In contrast to earlier thinking that brain disorders were either organic or functional, it is now clear that they all involve changes in gene activity. Some (heritable) disorders are due to alterations in gene structure. Other disorders result from epigenetic regulation of gene activity by enhancers and repressors.

Synaptic functioning is malleable throughout life:

In the developing brain, genetic and developmental programs regulate pathfinding, target recognition and the initial formation of synapses.

In the maturing brain, environmental inputs regulate the fine-tuning of synaptic connections.

In the adult brain, learning alters synaptic efficacy (gain control).

Relevant reading: chapter 63 in “Principles”