Molecular Mechanisms of Memory and Learning

Introduction

The neurobiology of memory focuses on identifying where and how different types of information are stored. Hebb's hypothesis that "cells that fire together, wire together" suggested that memory results from synaptic modification. More recent studies of simple invertebrates and electrical stimulation of brain show that measurable synaptic alterations underlie memories.

Procedural Learning

Procedural memories are amenable to investigation.

Non-associative Learning

- Habituation – Learning to ignore stimulus that lacks meaning
- Sensitization – Learning to intensify response to stimuli

Associative Learning

- Classical Conditioning – Pair an unconditioned stimulus (US) with a conditioned stimulus (CS) to get a conditioned response (CR)
- Instrumental (operant) Conditioning – Learn to associate a response with a meaningful stimulus
    - Involve more complex neural circuits related to role played by motivation

Invertebrate Models of Learning

Advantages of using invertebrate nervous systems include.

- Small nervous systems
- Large neurons
- Identifiable neurons
- Identifiable circuits
- Simple genetics

Non-associative Learning in Aplysia

Habituation of gill-withdrawal reflex

- Repeated stimulation of sensory neuron (from siphon) causes fewer quanta of glutamate to be released per action potential onto motor neuron
- Ca^{2+} channels become less effective

Sensitization of gill-withdrawal reflex

- Sensitizing stimulation of neuron L29 from head causes sensory neuron (from siphon) to release more quanta of glutamate per action potential onto motor neuron
- Involves an axoaxonic synapse between neuron L29 from head and sensory neuron from siphon
    - Serotonin released by stimulation of neuron L29 causes G-protein coupled activation of adenylyl cyclase in sensory axon terminal (synaptic bulb)
    - Cyclic AMP production activates protein kinase A
    - Phosphates attach to potassium channels, causing them to close
    - Decreased potassium conductance increases positive charge in axon terminal
    - Increased positive charge cause more calcium channels to open and more neurotransmitter release.

Associative Learning in Aplysia

- Classical conditioning: CS (sensory neuron from siphon) initially produces no response but after pairing with US (L29 from head) causes withdrawal
    - Pairing of CS and US causes greater activation of adenylyl cyclase because CS admits calcium into the presynaptic terminal

Vertebrate Models of Learning

Advantages of using invertebrate nervous systems include.

- Learning and memory can result from modifications of synaptic transmission
- Synaptic modifications can be triggered by conversion of neural activity into intracellular second messengers
- Memories can result from alterations in existing synaptic proteins

Synaptic Plasticity in the Cerebellar Cortex

The cerebellum is an important site for motor learning.

Anatomy of the cerebellar cortex

- Purkinje cells
    - Cell bodies in Purkinje cell layer
    - Dendrites extend into molecular layer
        - Each cell receives input from climbing fiber of one inferior olive cell
        - Each cell receives input from 1000s of different parallel fibers
    - Axons synapse on neurons of deep cerebellar nuclei (major output)
    - GABA is neurotransmitter
- Granule cells
    - Cell bodies in Granule cell layer
    - Dendrites remain in Granule cell layer (receive axons from
    - Axons extend as parallel fibers into molecular layer and synapse on dendrites of Purkinje cells
    - ____ is neurotransmitter

- Inferior Olive cells
  - Cell bodies in Inferior Olive
  - Dendrites receive information from muscle stretch receptors
  - Axons extend as climbing fibers into molecular layer of cerebellum and synapse on dendrites of Purkinje cells
  - ____ is neurotransmitter
- Pontine Nuclei cells
  - Cell bodies in Inferior Olive
  - Dendrites receive information from cerebral neocortex
  - Axons extend as mossy fibers into granule layer and synapse on dendrites of Granule cells
  - ____ is neurotransmitter

Long-Term Depression in the Cerebellar Cortex

- Pairing of climbing fiber stimulation with parallel fiber stimulation leads to a depressed response of Purkinje cells to parallel fiber stimulation – Long-term depression (LTD)
- Parallel fibers secrete glutamate and activate postsynaptic glutamate receptors
  - Increase internal Na+ concentration via AMPA receptors and activation of protein kinase C via metabotropic glutamate receptor
- Climbing fibers secrete _____ and activate Na+ channels
  - Depolarization activates Ca2+ channels and increases internal Ca2+ concentration
- Together causes internalization of AMPA receptors
  - Decreases opening of postsynaptic AMPA receptor channels