Synaptic Transmission

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Synaptic Transmission

- Biological process by which a neuron communicates with a target cell across a synapse

- *Synapse* is an anatomically specialized junction between two neurons, at which the electrical activity in a presynaptic neuron influences the electrical activity of a postsynaptic neuron

- Synapse can be between a neuron and a
  - Neuron
  - Muscle
  - Gland cell

Synaptic Transmission

- The average neuron forms several thousand synaptic connections and receives a similar number
  - The Purkinje cell of the cerebellum receives up to 100,000 synaptic inputs

- 10^{11} neurons, 10^{14} (100 trillion!) synapses

Synaptic Transmission

- *Electrical synapse transmission*: transfer of electrical signals through gap junctions

- *Chemical synaptic transmission*: release of a neurotransmitter from the pre-synaptic neuron, and neurotransmitter binding to specific post-synaptic receptors

Electrical Synapses

- Connection through gap junctions
  - Narrow gap between membranes (3 nm)
  - Connexin → connexon → gap junction
  - Direct ion passage from one neuron to another
  - Big enough for many small organic molecules to pass through (1-2 nm)
  - Mostly between dendrites

Electrical Synapses

- Electrical postsynaptic potential (PSP) induced by ionic current flow (1 mV or less)

Electrical Synapses

- Advantages
  - Extremely rapid
  - Orchestrating the actions of large groups of neurons
  - Can transmit metabolic signals between cells

- Less common in vertebrate nervous system
  - Require a large area of contact; restricting number of synaptic inputs
  - Cannot be inhibitory

Electrical Synapses

- Found where normal function requires that the activity of neighbouring neurons be highly syncronized
  - During prenatal and postnatal brain development, neigbouring cells share both electrical and chemical signals to coordinate their growth and maturation
  - Hormone-secreting neurons within the hypothalamus to facilitate a burst of hormone secretion into the circulation

Chemical Synapses

- No structural continuity
  - Synaptic cleft (20-40 nm)
  - Diffusion of neurotransmitters

- Presynaptic terminals contain 100 to 200 synaptic vesicles, each filled with several thousand molecules of the neurotransmitter

- The synaptic vesicles are clustered at *active zone*s

Chemical Synapses

- *Cell Adhesion Molecules (CAMs)*
  - proteins in the pre- and postsynaptic membranes that project from these membranes into the synaptic cleft, where they bond to each other
- Ensures that the pre- and postsynaptic membranes stay in close proximity for rapid chemical transmission

Presynaptic Terminal

- *Terminal boutons*
- Voltage-gated Ca^{2+} channels
- Ca^{2+} influx
- Fusion of vesicles
  - Synaptic vesicles (neurotransmitter)
  - Secretory granules (neuropeptides)
- Exocytosis

Presynaptic Terminal

- Vesicles are docked in the active zones by the interaction of proteins
  - SNAREs
- Ca^{2+} interaction with synaptotagmin
- Conformation change in the SNARE complex
- Membrane fusion

- Botulinum toxins targets excitatory synapses that release ACh as a neurotransmitter and digests one of the SNAREs

- Muscles are unable to contract (flaccid paralysis)

Presynaptic Terminal

- Vesicles completely fuse with the membrane and are later recycled by endocytosis from the membrane at sites outside the active zone

- At synapses with high action potential firing frequencies, vesicles fuse briefly then reseal the pore and withdraw back into the axon terminal (“kiss-and-run fusion”)

Synaptic Cleft

- Neurotransmitter diffusion
- 20-40 nm
- Neurotransmitters rapidly and reversibly bind to receptors on the plasma membrane
  - Bound ligand is in equilibrium with the unbound form

Synaptic Cleft

- Unbound neurotransmitters are removed from the synaptic cleft
  1. actively transported back into the presynaptic axon terminal for reuse (reuptake)
  2. transported into nearby glial cells where they are degraded (astrocytes)
  3. diffuse away from the receptor site
  4. enzymatically transformed into inactive substances

Postsynaptic Terminal

- *Postsynaptic density:* area with high protein accumulation under the postsynaptic membrane

  (receptors)

- *Neurotransmitter receptors:* convert intercellular chemical signal (i.e., neurotransmitter) into an intracellular signal (i.e., a change in membrane potential or a chemical change)

Postsynaptic Neuron

- *Synaptic delay* (at least 0.3 msec) between the arrival of an action potential at a presynaptic terminal and the membrane potential changes in the postsynaptic cell

Types of Synaptic Contacts

- Axodendritic: Axon to dendrite
- Axosomatic: Axon to cell body
- Axoaxonic: Axon to axon
- Dendrodendritic: Dendrite to dendrite

CNS Synapses

- Excitatory synapses
  - Gray's type I morphology, Asymmetrical
  - Spines: Excitatory synapses
- Inhibitory synapses
  - Gray's type II morphology, Symmetrical
  - Clustered on soma and near axon hillock

Synapses Vary in Size and Strength

- Larger synapses allow the presynaptic neuron to have a larger and more reliable effect on the postsynaptic neuron

Neurotransmitter Receptors

- All receptors for chemical transmitters have two biochemical features in common:
  1. They are membrane-spanning proteins. The region exposed to the external environment of the cell recognizes and binds the transmitter from the presynaptic cell.

  2. They carry out an effector function within the target cell. The receptors typically influence the opening or closing of ion channels.

Neurotransmitter Receptor Types

Ionotropic receptors

- Ion channels
- Direct change in ion movement across the plasma membrane of postsynaptic cell
- Fast, short-lived responses

Metabotropic receptors

- Not ion channel
- Induce signalling cascade in the postsynaptic cell that leads to changes in ion channels
- Slow and longer-lived responses

Autoreceptors and Presynaptic Inhibition

- Receptors are sometimes found on the presynaptic terminal.
- Activation leads to:
  - Inhibition of neurotransmitter release
  - Neurotransmitter synthesis.
- Autoreceptors may act as a brake on the release of neurotransmitters

Neurotransmitter Receptors

Postsynaptic Receptors Gate Ion Channels Either Directly or Indirectly

- *Ionotropic receptors:* the receptor undergoes a conformational change that opens the channel.

- *Metabotrobic receptors:* alter intracellular metabolic reactions. Production of second messengers (cAMP, DAG), activates protein kinases (PKA) that phosphorylates ion channels, leading to their opening or closing

Neurotransmitter Receptors

- Ionotropic receptors
  - produce relatively fast synaptic actions lasting only milliseconds
  - found at synapses in neural circuits that mediate rapid behaviors, (e.g., stretch receptor reflex)

- Metabotropic receptors
  - produce slower synaptic actions lasting seconds to minutes
  - can modulate behavior by altering the excitability of neurons and the strength of the synaptic connections of the neural circuitry mediating behavior, (e.g., learning)

Neurotransmitter Receptors

- For ions, transmitter-gated channels are not as selective as voltage-gated channels.
  - ACh-gated ion channels at the neuromuscular junction are permeable to both Na^+ and K^+

- If the open channels are permeable to Na^+, the net effect will be to depolarize the postsynaptic cell from the resting membrane potential

Neurotransmitter Receptors

- Both electrical and concentration gradients drive Na+ into the cell, whereas for K+ , the electrical gradient opposes the concentration gradient

- Opening channels that are permeable to both ions results in the simultaneous movement of a relatively small number of potassium ions out of the cell and a larger number of sodium ions into the cell

- The net movement of positive ions is into the postsynaptic cell, causing a slight depolarization.

Postsynaptic Potentials

- *Excitatory postsynaptic potential (EPSP)* a transient postsynaptic membrane depolarization

- EPSP is a depolarizing graded potential that decreases in magnitude as it spreads away from the synapse by local current

Postsynaptic Potentials

- *Inhibitory postsynaptic potential (IPSP)* a transient postsynaptic membrane hyperpolarization

- Activated receptors on the postsynaptic membrane open Cl^- or K^+ channels

Neuropharmacology

- Effect of drugs on nervous system tissue
- *Receptor antagonists*: Inhibitors of neurotransmitter receptors
  - Curare
- *Receptor agonists*: Mimic actions of naturally occurring neurotransmitters
  - Nicotine
- Defective neurotransmission: Root cause of neurological and psychiatric disorders

Termination of Neurotransmitter Signaling

- After a response is triggered, the chemical synapse returns to its resting state

- The neurotransmitter molecules are cleared from the synaptic cleft
  - Enzymatic clearence
  - Diffuse away from the cleft
  - Active transport back to the presynaptic terminal