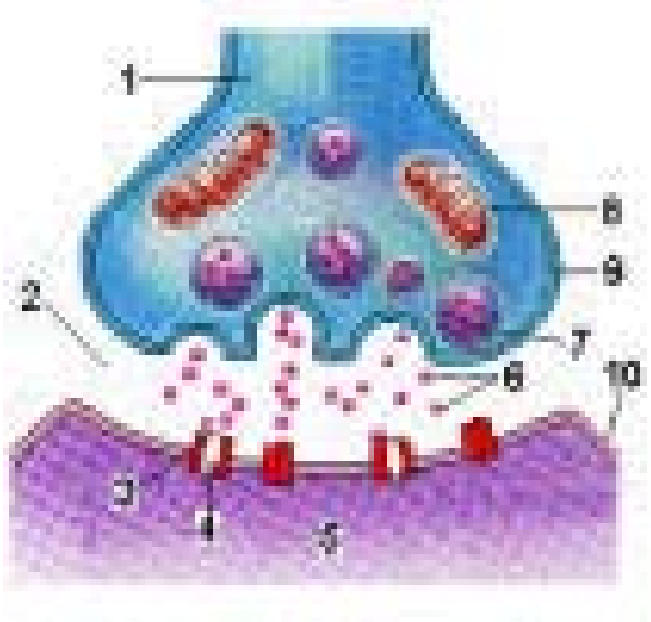
SYNAPTIC TRANSMISSION



Study material for B.Sc (H) Physiology 2nd Sem

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Review ~ Setting the Stage

- Information is digitized at the axon hillock and a stream of action potentials carries the output of a neuron down the axon to other neurons.
- Neurons are the only class of cells that do not touch neighboring cells.
  - How is this output transferred to the next neuron in the chain?
- The transfer of information from the end of the axon of one neuron to the next neuron is called *synaptic transmission*.

Moving the Message

- Transmission of the signal between neurons takes place across the *synapse*, the space between two neurons.
- In higher organisms this transmission is chemical.
- Synaptic transmission then causes electrical events in the next neuron.
- All the inputs coming into a particular neuron are integrated to form the generator potential at its axon hillock where a new stream of action potentials is generated.

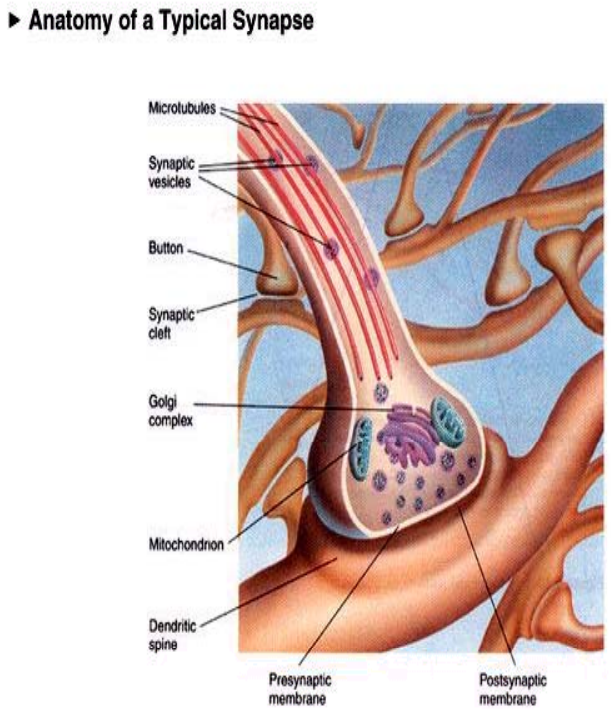
Synaptic Connections

- Neurons are the only cells that can communicate with one another rapidly over great distance
- Synaptic connections are specific.
  - Underlie perception, emotion, behavior
  - The average neuron makes 1000 synaptic connections - receives more
  - The human brain contains 10^{11} neurons & forms 10^{14} connections
- Neural processing occurs from the integration of the various synaptic inputs on a neuron into the generator potential of that neuron.

Special Channels

- Recall the 2 classes of channels for signaling within cells:
  - Resting channels that generate resting potential
  - Voltage-gated channels that produce an action potential
- Synaptic transmission uses 2 additional classes of channels:
  - Gap-junction channels
  - Ligand-gated channels

Composition of a Synapse



- The synapse is made of 3 elements:
  - pre-synaptic terminal
  - postsynaptic cell
  - zone of apposition

Types of Synapses

- Synapses are divided into 2 groups based on zones of apposition:
- Electrical
- Chemical
  - Fast Chemical
  - Modulating (slow) Chemical

Electrical Synapses

- Common in invertebrate neurons involved with important reflex circuits.
- Less common in adult mammalian neurons, but common in many other body tissues such as heart muscle cells.
- Current generated by the action potential in pre-synaptic neuron flows through the gap junction channel into the next neuron
- Send simple depolarizing signals
- May transmit metabolic signals between cells

Properties of the Electrical Synapse

- Two cell membranes are aligned parallel
- The synaptic cleft is small ~3.5 nm
- Usually between large presynaptic neuron & small postsynaptic neuron
  - takes a lot of current to depolarize a cell
- Specialized proteins called *connexons* span the pair of membranes to make a very large pore (the *Gap Junction Channel*)
- Signal can be bi-directional

Gap-junction Channels

- Connect communicating cells at an electrical synapse
- Consist of a pair of cylinders (*connexons*)
  - one in presynaptic cell, one in post
  - each cylinder made of 6 protein subunits
  - cylinders meet in the gap between the two cell membranes
- Always open
  - All ions and many small organic molecules are free to pass through the pore
- Gap junctions serve to *synchronize* the activity of a set of neurons

Synchronizing Cells

- Electrical transmission allows rapid, synchronous firing of interconnected cells
  - Can interconnect groups of neurons
- Very fast; virtually no delay
  - Speed important for certain responses - defense
- Electrically coupled cells can trigger explosive, all or none behavior
- Adaptive advantage (e.g. goldfish tail, squid ink)

Modulating Conductance

- Gap junctions close in response to lower cytoplasmic pH or increased Ca^{+2}
- Some act as rectifiers
  - channels are sensitive to voltage
  - therefore transmission unidirectional
- Linkage to chemical synapses
  - neurotransmitters released from nearby chemical synapses can activate 2^{nd} messenger dependent enzymes that alter gating of gap junction channels

Chemical Synapses

- Synaptic cleft is larger
- There is no structural continuity between presynaptic & postsynaptic cells
- A chemical molecule, a ***neurotransmitter***, is released from the presynaptic neuron
  - diffuses across the synaptic cleft (20-50 nm)
  - binds with a receptor on the postsynaptic membrane.

Categories of Chemical Synapses

- Fast chemical synapses:
  - Have *transmitter-gated ion channels*
  - Fast, electrical response to arrival of presynaptic action potential
  - Use amino acids and amines as neurotransmitters
- Slow, modulatory chemical synapses:
  - Have G-protein-coupled ion channels
  - Slow response to arrival of presynaptic action potential
  - activate second messenger system; not always a direct electrical effect
  - May use amino acids, amines, or peptides

Structure of the Chemical Synapse

- Presynaptic structures:
  - Vesicles - contain amino acids or amines, released at synapse
  - Secretory granules (dense-cored vesicles) - contain peptides
  - Presynaptic densities - serve to organize vesicles and prepare them for release
- Postsynaptic structures:
  - Postsynaptic densities - loaded with receptors and ion channels, bind neurotransmitters and establish ionic currents

Wiring Patterns of Chemical Synapses

- *Axosomatic synapse* - Axon terminal ends on a cell body
- *Axodendritic synapse* - Axon terminal ends on a dendrite
- *Axoaxonic synapse* - Axon terminal ends on another axon
- *Dendrodendritic synapse* - Dendrite makes synapse with another dendrite

Release of Neurotransmitters

- Occurs in response to Ca^{+2} influx that occurs with the action potential
- Change in membrane potential in presynaptic neuron leads to release of chemical transmitter from terminals
  - transmitter diffuses across cleft
  - binds to receptor molecules on the postsynaptic cell membrane
  - binding receptor causes ion channels to open or close, altering potential

Transmitter Binding

- Binding receptor is specific - lock & key
- Action determined by properties of receptor, not chemical properties of the transmitter
  - receptor determines if response is excitatory or inhibitory
- All neurotransmitter receptors have 2 biochemical features in common:
  - they are membrane spanning proteins that recognize & bind transmitter
  - they carry out effector function with a target cell, usually by influencing opening or closing of ion channels

Synaptic Release
Fast Chemical Synapses

- Action potential invades axon terminal
- Voltage-gated calcium channels pop open
- Calcium ions flood presynaptic terminal in region of vesicle release
- Synaptic vesicles fuse with presynaptic membrane – exocytosis
- Neurotransmitter molecules diffuse into and across synaptic cleft

Transmitter-Gated Ion Channels

- Neurotransmitter molecules bind to the receptor site on transmitter-gated ion channels embedded in the postsynaptic membrane
- Ionic currents flow into or out of the postsynaptic cell
- If Na^+ ions are the carrier, the membrane potential of the postsynaptic cell is depolarized
  - **EPSP** -Excitatory Post-Synaptic Potential
- If Cl^- ions or K^+ ions are the carrier, the membrane potential of the postsynaptic cell is hyperpolarized
  - **IPSP** - Inhibitory Post-Synaptic Potential

Removal of Neurotransmitter

- The neurotransmitter is inactivated or removed from the synaptic cleft
- For acetylcholine, there is an enzyme, acetylcholine esterase (AChE) that does this
- For other amino acids and amines, the presynaptic membrane actively sucks up the transmitter and neighboring glial cells may do likewise

Synaptic Release Neuromodulatory Synapses

- Action potential invades axon terminal
- Voltage-gated calcium channels pop open
- Calcium ions flood presynaptic terminal in region of vesicle release
- Synaptic vesicles fuse with presynaptic membrane – exocytosis
- Neurotransmitter molecules diffuse into and across synaptic cleft
- Neurotransmitter molecules bind to receptor proteins in the postsynaptic membrane

G-Protein-Coupled Receptors

- G-proteins in the membrane are activated and move along inner face
- Activated G-proteins activate effector proteins
- May act directly or indirectly (2^{nd} messenger)
- The neurotransmitter is inactivated or removed from the synaptic cleft

Direct Receptors

- Ionotropic
- Are membrane spanning
- Made of several peptide subunits
- On binding neurotransmitter, undergo conformational change that opens a G-protein gated ion channel
- Example - acetylcholine receptor on muscle

INDIRECT RECEPTORS

- Are macromolecules that are separate from the ion channels on which they act
- 2 famililes:
- Metabotropic
  - membrane spanning proteins
  - a single polypeptide chain coupled to GTP-binding proteins, which activate enzymes that produce 2nd messenger such as cyclic AMP
  - 2nd messenger either acts on channel directly or thru enzyme
- Tyrosine kinase family
  - add a phosphate group to tyrosine of substrate proteins, modulating channel

Synaptic Integration: Fast Chemical Synapses~ Gated Ion Channels

- Synaptic transmitter release is *quantal*
  - Each vesicle or secretory granule contains the same number of neurotransmitter molecules
  - The EPSP or IPSP that results is one of a set of consistent sizes - one vesicle, two vesicles, three vesicles, etc.
  - Typically at a neuromuscular junction 200 vesicles are released from one action potential - fail safe contraction of the muscle
  - At a synapse in the CNS, typically only one vesicle is released - input for processing in the dendrite
- Not every synaptic release causes an action potential in the postsynaptic neuron

Spatial Summation

- The dendrites of each neuron receive many synaptic inputs from a variety of neurons.
- The combining of the EPSPs and IPSPs across the dendrite from the simultaneous arrival of action potentials at various synapses is called *spatial summation*

Length Constant

- The measure of how effective a given synapse is in contributing to spatial summation
- The length constant gives the distance (in μm) that it takes an EPSP or IPSP to decrease to 37% of its original value at the synapse:
- The length constant is directly proportional to the membrane resistance and inversely proportional to the longitudinal resistance of the cytoplasm
  - The leakier the membrane, the shorter the length constant
  - The narrower the dendrite, the shorter the length constant

Temporal Summation

- The combining of EPSPs or IPSPs from repeated action potentials arriving at a single synapse is called temporal summation
- The measure of how effective a given synapse is in contributing to temporal summation is the time constant, t
- The time constant gives the time (in milliseconds) that it takes an EPSP or IPSP to decrease to 37% of its original value at the synapse
- In most cases, the effects of spatial summation and temporal summation must both be taken into account

NEUROMODULATION

- With a G-protein-coupled receptor, a chain of events is triggered that usually ends with the phosphorylation of a protein.
- For example:
  - When a receptor for norepinephrine is activated,
  - a G-protein is activated.
  - Adenyl cyclase (an enzyme) is activated, which
  - uses ATP to produce cyclic AMP, a second messenger.
  - cAMP activates a protein kinase.
  - The protein kinase phosphorylates a potassium channel,
  - Which causes it to close
- This increases l and t, thereby making synapses more potent for a period of time
  - hence the term modulation

Why Chemical Transmission?

- More flexible; produces more complex behaviors
- Plasticity
- Can amplify neuronal signals
- Directly gated are comparatively fast
  - mediate behavior
- Indirect are slower
  - important in memory, learning

Flexibility of Chemical Transmission

- Produces more complex behaviors
- Same neurotransmitter can have several functions
  - at one terminal can be released at the active zone & serve as a direct transmitter, acting on neighboring cells
  - at another site can serve as a modulator
  - at a third site released into bloodstream as neurohormone

Plasticity of Chemical Transmission

- Chemical Transmission has plasticity plasticity because it is multistep
- Important for memory & other higher functions
- Modifiability of chemical synapses is an important mechanism in behavioral learning

Amplifying Neuronal Signals

- Chemical transmission can amplify neuronal signals
- A small nerve terminal can alter the potential of a large postsynaptic cell
- The action of just one synaptic vesicle leads to opening of thousands of ion channels