SYNAPTIC TRANSMISSION

Study material for B.Sc (H) Physiology 2nd Sem
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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 \textit{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
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 2nd 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
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- 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-COUPL ED 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\textsuperscript{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 families:

- 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 I 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 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