Synaptic Transmission

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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

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

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)

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

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

Synaptic Integration

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Summation of Postsynaptic Potentials

- The cell body of a postsynaptic neuron may receive inputs from hundreds or thousands of synaptic terminals

- A single EPSP is usually too small to trigger an action potential in a postsynaptic neuron

- *Synaptic integration* is the process by which multiple synaptic potentials combine within one postsynaptic neuron

- At the neuromuscular junction, single action potential in the presynaptic terminal triggers the exocytosis of about 200 synaptic vesicles, causing an EPSP of 40 mV or more.

- At many CNS synapses, the contents of only a single vesicle are released in response to a presynaptic action potential, causing an EPSP of only a few tenths of a millivolt

Summation of Postsynaptic Potentials

- Individual postsynaptic potentials can combine to produce a larger potential in a process called *summation*
  - At the axon hillock (high number of Na+ channels)

Summation of Postsynaptic Potentials

- In *spatial summation*, EPSPs produced nearly simultaneously by different synapses on the same postsynaptic neuron add together

- If two EPSPs are produced in rapid succession (1-15 msec) by the same synapse, an effect called *temporal summation* occurs

- Dendrite membranes are electrically passive –lacks voltage gated channels

- Exception; apical dendrites of pyramidal cells of the cerebral cortex

Synaptic Inhibition

- Most synaptic inhibition is mediated by GABA-gated Cl- channels
  - E_{Cl-} is -65 mV
  - If membrane potential is less negative than -65mV, GABA mediates hyperpolarizing IPSP
- Two Mechanisms
  - Hyperpolarization
  - Shunting Inhibition: Inhibiting current flow from dendrites and soma to axon hillock

Shunting Inhibition: Inhibiting current flow to axon hillock

- Increasing membrane conductance will decrease membrane length constant
- Opening any channel will cause an EPSP to decay over a shorter distance
- *Shunting inhibition:* It prevents depolarizing current from reaching the axon hillock and eliciting an action potential.
- *the inward movement of negatively charged chloride ions*

Synaptic Modulation

- Synaptic transmission that modifies effectiveness of EPSPs generated by other synapses

- Activating NE β-receptors
  - Close K^+ Channels

  - Decreasing the K^+ conductance increases the dendritic membrane resistance and therefore increases the length constant

  - Distant or weak excitatory synapses will become more effective in depolarizing the spike-initiation zone beyond threshold; the cell will become more excitable

Synaptic Plasticity

Synaptic Plasticity

- The strength of a synapse can change; it is “plastic”
  - A neuron can therefore select its own synapses
- Synaptic plasticity is thought to be the main mechanism of learning and memory

Learning

- Glutamate is the most common excitatory neurotransmitter in nervous system

- Ionotropic glutamate receptors
  - AMPA
    - Rapid influx of Na+
  - NMDA
    - Slow and longer lasting influx of Na+ and Ca^{2+}
    - Requires previous depolarization

- At rest NMDA receptors are blocked by Mg2+
- Depolarization by AMPA removes Mg2+ block
- Na+ and Ca2+ influx through NMDA
- Cellular and gene changes triggered by Ca2+
- By repeted high-frequency stimulation the magnitude of the postsynaptic response is enhanced (long term potentiation-LTP)

Neural Circuits

- Complex neural circuits are possible because of associations such as convergence and divergence

Convergence

- A single neuron is affected by converging signals from two or more presynaptic neurons
    - Allows CNS to integrate incoming information from various sources

Divergence

- A single presynaptic neuron stimulates many postsynaptic neurons
    - Allowing widespread effect

Reverberating Circuits

- Important in
  - rhythmic breathing
  - mental alertness
  - short-term memory

- Depend on positive feedback
  - new impulses generated again and again until synapses fatigue

EEG
Electroencephalography

- Recording of the electrical activity of the brain
- Graphic representation of the difference in voltage between two different cerebral locations plotted over time

Electroencephalography

- The EEG is the recording of the electrical activity generated by cerebral neurons from scalp.
- Depth of only 0.3-0.6 mm

Electrical Activity Types in a Neuron

Action Potentials

- discrete voltage spikes that travel from the beginning of the axon at the cell body to the axon terminals, where neurotransmitters are released

Postsynaptic Potentials

- voltages that arise when the neurotransmitters bind to receptors on the membrane of the postsynaptic cell, causing ion channels to open or close and leading to a graded change in the potential across the cell membrane

Neural basis of the EEG

To pick up the electrical activity of the brain from scalp recordings, it must be of sufficient strength and duration…

Action Potentials…?

Rapid, transient, all-or-none nerve impulses of 100mV aprox. and a duration of 1ms that flow from the body to the axon terminal of a neuron.

They don’t create a dipole

- Surface electrodes cannot detect action potentials due to the timing of the action potentials and the physical arrangement of axons.
  - Because neurons rarely fire at precisely the same time, action potentials in different axons will typically cancel each other.

	Action potential	Postsynaptic potential
Amplitude	100 mV	10 mV
Period	1 ms	10 ms

Neural basis of the EEG

When an EPSP is generated in the dendrites of a neuron an extracellular electrode detects a negative voltage difference, resulting from Na^+ currents flowing inside the neuron's cytoplasm.

The current completes a loop further away the excitatory input (Na^+ flows outside the cell), being recorded as a positive voltage difference by an extracellular electrode.

a small dipole is generated

- The dipole from a single neuron is so small to be recorded over the scalp.
- If the dipoles from many neurons summate it will be possible to meausure the resulting voltage from scalp.
- To be summated they must occur at approxiamately the same time across thousand or millions of neurons, and the dipoles from individual neurons must be spatially aligned.
    - If the neurons all have a similar orientation and all receive the same type of input, their dipoles will summate and may be measurable at the scalp. This is most likely to occur in cortical pyramidal cells, which are aligned perpendicular to the surface of the cortex.

EEG records Postsynaptic potentials: apical dendrites of pyramidal neurons

- Duration of postsynaptic potentials is longer than action potentials
- Confined to the dendrites and cell body and occur essentially instantenously rather than traveling down the axon
- Creates a dipole

- PSPs summate rather than cancel, making it possible to record them at a great distance.

Why EEG?

- Excellent temporal resolution (1 msec)
- Non-invasive

Volume conduction

- When a dipole is present in a conductive medium (i.e., brain), current is conducted throughout that medium until it reaches a surface. (volume conduction)

- The voltage that will be present at any given point on the surface of the scalp will depend on the position and orientation of the generator dipole and also on the resistance and shape of the various components of the head (brain, skull, scalp)

Inverse Problem

Electric fields are smeared by the resistance of the skull.

Volume Conduction

- EEG is a 2-D representation of a 3-D reality, which poses a problem in localizing the sources of the electrical activity

Inverse problem

- Forward problem is easy to solve
- Inverse problem is “underdetermined”
  - An infinite number of different dipole configurations can produce any given voltage distribution
  - It is impossible to know with certainty which one of the configurations can produce any given voltage distribution