

Fundamentals of Neuroscience, Part 2: Neurons
and Networks Harvard X - MC B80.2X.

* Boundary between 2 neuron that is one neuron and dendrite of another is called a "synapse" \rightarrow escape reflex (ex)

2 types of synapse:

① Electrical synapse (complex) (less common in Brain & Reflex arc the heart):

\rightarrow Electrical synapse are pores b/n 2 cells which allow the passage of electrical signal to a neighbouring cell

\rightarrow Fast and high degree of synchronicity

\rightarrow Signal flow both way-

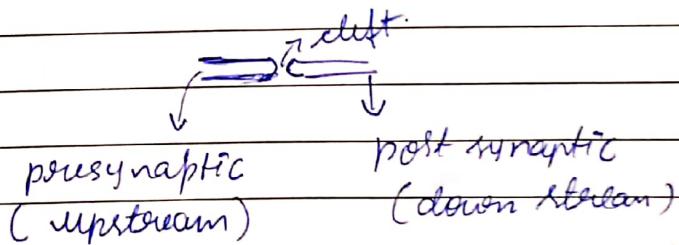
② Chemical synapse:

\rightarrow Complex and common in humans

\rightarrow Action potential travel to the end of the axon and cause a chemical to be released to small space b/n 2 neurons called synaptic cleft. This chemical signal can cause down stream neuron to other side of the cleft to depolarize its membrane, converting the chemical signal back into an electrical one

\rightarrow Slower.

\rightarrow cleft - 20 - 40 nm.



\rightarrow diversity due to neurotransmitters, neuromodulators, receptors

\rightarrow "chemical signal that tell the post-synaptic neuron to increase/decrease their likelihood of firing is neurotransmitter"

\rightarrow Ensure directionality. \Rightarrow One direction

\rightarrow May require more action potential summed to fire up in the post-synaptic cell.

- Receptors are chemically gated ion channels.
- In chemical synapse a single synapse can cause different outcomes at receptor by changing neurotransmitter released
- Diffusion is the force that brings neurotransmitters from presynaptic side of the synaptic cleft to the postsynaptic side.

* Steps in synaptic transmission in broad stroke,

- ① Action potential travels down the axon to the synapse.
- ② When depolarized the signal arrives at the presynaptic terminal introduces a release of pre-made neurotransmitters / neural modulator into synaptic cleft. These molecules are packaged into structures called vesicles and are made of same material as cell membrane, its job is to hold the small quantity of signalling molecule at the ready.
- ③ The above molecules then diffuse across the cleft and bind to specific molecule called receptors on the other side of the cleft on the postsynaptic terminal.

* Terminology

EPP (for Katz) - End plate potential

↳ for this fig (Katz)

(EPSP) ↗

Excitatory: Neuron is more likely to fire

Presynaptic

Post synaptic
(here muscle fibre)

Posynaptic potential

-55mV Threshold voltage

exciting potential

-65mV

Inhibitory: (IPSP)

Received signal makes neuron less likely to fire

Acetylcholine \rightarrow primary neurotransmitter at the ~~neuro-muscular~~
junction.

CLASSMATE

Date _____

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Absorb the blips

- \Rightarrow Drug cocaine blocks acetylcholine receptors and prevents acetylcholine from activating the post-synaptic receptors.
- \Rightarrow Nostigmine blocks the enzyme acetylcholinesterase, the enzyme which breaks down acetylcholine. thus increasing the amplitude and duration of EPPs.
water *blips larger*
- \Rightarrow NMJ : Neuro muscular junction
- * Concentration of different ions around NMJ and observe the effect on the synapse.
 - \Rightarrow Calcium is injected right around pre-synaptic terminal. (In vitro preparation).
 - \Rightarrow This contains $[Ca^{+2}]$ EPP. amplitude
 - $\boxed{\text{Amplitude of EPP} \propto [Ca^{+2}]^4}$
 - \Rightarrow Stimulating just after precise concentration and timing
- \Rightarrow Vesicles are the source of quanta that Katz observed.
- \Rightarrow Greater Ca^{+2} concentration inside the cell makes the probability of neurotransmitter release more likely.

Neurotransmitters are packaged into vesicles that contain hundreds of molecules that are released all at once.
- \Rightarrow Synaptosomal protein is a protein which is found in very high concentrations in synaptic vesicles.

Axon at presynaptic depolarizes \rightarrow Ca^{+2} channel open \rightarrow
 Ca^{+2} flow in \rightarrow Ca^{+2} makes 'V' and 't' SNARE's ^{classmate} interact
and then fuse tog other.

\rightarrow When an action potential arrives at the presynaptic terminal, the voltage gated Ca^{+2} channels are opened. The influx of Calcium triggers the fusion of synaptic vesicles with the presynaptic membrane, allowing release of neurotransmitter into synaptic cleft. This vesicle fusion happens by the action of SNARE protein complex.

\rightarrow Vesicle fusion in a synapse \rightarrow Vesicle associated snare protein (V-snare)

Snare protein on membrane \rightarrow T-SNARE

Ex: Synaptotagmin \rightarrow V-SNARE.

SNARE 25 and syntoxin \rightarrow t-SNARES.

* 5 fates of neurotransmitter after released:

① A nerve transmitter molecule can travel across synaptic cleft and bind to its dedicated receptor on the other side.

Travel speed of neurotransmitter - 0.05 miles/hr

\rightarrow Transmitting at specific time is important.

\rightarrow If a neurotransmitter were allowed to remain in synaptic cleft for too long it could bind and unbind to its dedicated receptor and potentially activate the post synaptic cell multiple times before diffusing out of synaptic cleft

Mechanisms are needed to shut off neurotransmitter action in the synaptic cleft before simply diffusing away. 4 mechanisms are.

① Crossing synaptic cleft binding to its dedicated receptor

② Neurotransmitter can be broken down by specific enzymes that are present in the synaptic cleft.

③ Neurotransmitter can be taken up by specific transporter proteins present on the surface of

glia cells that surround and even sometimes invade the synaptic cleft.

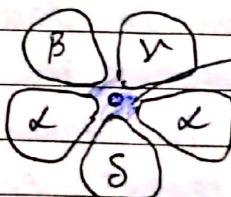
④ Combination of all above mentioned can also happen.

* Classification of synapses:

- ① Strong vs. weak. (post-synaptic neuron to integrate incoming signal)
- ② Fast vs. slow. (duration of signal)
- ③ Excitatory vs. inhibitory. (depolarization or hyperpolarization of membrane potential).
- ④ Electrical vs. chemical.

- Multiple action potentials fired in a postsynaptic cell in short succession can sum up EPSP.
- Fast excitatory postsynaptic potentials are mediated primarily by cation-selective ion channels.
- Inhibitory postsynaptic potentials are mediated primarily by anion selective ion channels.
- Acetylcholine is a neurotransmitter that is released at the neuromuscular junction. Once released by axon terminal of the motor neuron, acetylcholine molecules cross the synaptic cleft and interact with nicotine receptors at the surface of the motor end plate, this resulting end plate leads to muscle contraction.

The acetylcholine receptor is a ligand-gated ion channel, it opens when specific chemical ligand binds to it.



ionotropic

central pore 0.8 nm wide



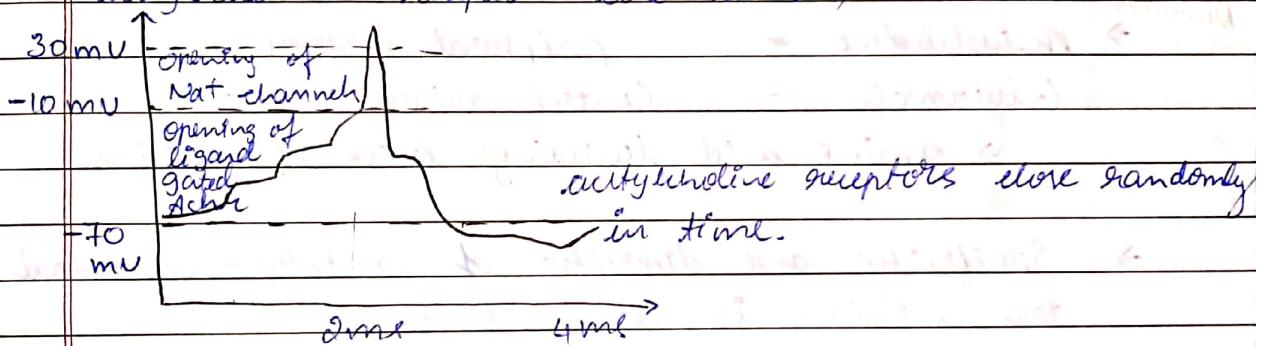
Extracellular

Intracellular

Binding of acetylcholine to the binding sites on the two alpha subunits on the acetylcholine receptor causes the ion channel to open. Both the binding site should be filled in order to open ion channel.

Current generated by single acetylcholine receptor equates to approximately 2 pico amps. (2 pA).

Typical synaptic current at neuromuscular junction equates to approximately 600,000 pA. (i.e. 300,000 acetylcholine receptors are active)



(nicotine receptor)

Acetylcholine receptor is a promiscuous cation channel with conductance of both K^+ and Na^+ and small amount of Ca^{2+} as well. Central pore of the channel is lined predominantly with -ve charged amino acids from the M2 subunit.

\hookrightarrow Na^+ move inwards, K^+ move outwards

\hookrightarrow There is reversal potential (-10 mV).

Average of sum of Nernst potential of Na^+ , K^+

Efficient removal of neurotransmitter molecule from the synaptic cleft is very important to avoid unwanted excitation and inhibition to occur. This happens by individual ions clearing them - others this process is called deactivation.

- Succinylcholine is a muscle relaxant : it causes desensitization of acetylcholine receptor
- Myasthenia gravis is an autoimmune disorder that leads to severe muscle weakness and fatigue because of blockade / destruction of acetylcholine receptors at the postsynaptic neuromuscular junction.
- Congenital myasthenic syndrome (CMS) is an inherited neuromuscular disorder caused by defects of the proteins that make up the neuromuscular disorder causing junction.

Neurotransmitters (EPSP)

(PNS)

→ Acetylcholine = peripheral nervous system

Glutamate - central nervous system

α amino acid building block of proteins.
glutamic acid

- Specificity and diversity of excitatory neuronal transmission is determined by,
 - Ionotropic receptors (fast flx)
 - metabotropic receptors.
 - G-protein coupled receptors. (GPCR)

* Ionotropic glutamate receptors } AMPA . Central Nervous
NMDA . System (CNS)

NMDA

AMPA

n-methyl-d-aspartate → α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor

→ ligand binding and change in membrane potential → ligand gated ion channels

→ synaptic plasticity

→ non selective to cations learning and memory function

* Coincidence detectors: when membrane at rest NMDA receptor has magnesium ion blocking its central pore. NMDA interaction is voltage dependent which needs initial depolarization to have a chance to open. This " " is brought by AMPA receptor. ∴ NMDA receptors are called coincidence detectors.

* Inhibitory synapses (IPSP's): Activation of inhibitory synapses results in a decreased likelihood of firing action potential. This is due to action of ligand gated ion channels including the GABA and glycine receptors.

→ The structure is similar to nicotinic acetylcholine receptors but the difference is no domain in each receptor subunit is lined by either +ve or neutral charged amino acids.

→ Both GABA and glycine receptors are anion selective ion channels causing an increase in chloride conductance.

→ When neurotransmitters are trying to depolarize a single postsynaptic neuron simultaneously, inhibitory synapses can maintain a neuron at or close to resting potential such inhibition mechanism is called shunting. (Cl-conducting) CNS

(Cl-conducting) Peripheral nervous system

→ Glycine is used in spinal cord instead of GABA

→ Steychnine, a component of rat poison is a very powerful antagonist of the Glycine receptor

* Positive allosteric modulation: It occurs when barbiturates in the central nervous system make GABA receptors more likely to get activated by binding outside the normal ligand binding site on the receptor.

- * One of the inhibitory disease is hyperekplexia which is characterized by exaggerated startle response to touch or acoustic.

Caused by genes encoding both presynaptic and postsynaptic proteins.

Hyperekplexia, defective glycine nerve transmission can be restored by treatment with clonazepam, which increases the inhibitory effect of GABA-related neurotransmission.

- * Action potential down the axon is regenerative process meaning action potentials keep constant amplitude from the initial segment to the presynaptic terminal. This is due to the presence of voltage-gated Na^+ and K^+ channels at the axon membrane.

⇒ Propagation of EPSP's along the dendrite tree is not a regenerative process as dendrites have no Na^+ or K^+ voltage gated channels.

Dendrite shaft, Soma, initial segment of the axon

⇒ Inhibitory inputs often occur on the cell body of the neuron even on axon initial segment.

⇒ Excitatory inputs tend to occur in the dendritic arbor. Dendritic spine

⇒ For maximum effect, inhibitory synapses must be closer to the cell body than excitatory synapses.

⇒ Inhibitory input hardly changes resting potential.

- * Convergence: when multiple potentially discrete inputs come together to synapse on a single downstream neuron.

* Divergence: One neuron sends a signal to many
example for

→ The myotatic reflex is simple pure convergence and divergence in the nervous system.

* Recurrence: Describes the situation where some chain of connected neurons ^(feedback) loop back onto itself.

A recurrent connectivity pattern that causes 2 or more populations of neurons to fire in a rhythmic way, out of phase.

* Neuromodulation: Process by which the synaptic transmission between 2 neurons is either enhanced or decreased through the action of third substance called neuromodulator.

* Efficacy: Changing synaptic strength without affecting the structure of the synapses.

→ Change in presynaptic through neuromodulation is via alteration in the number of neurotransmitter molecules released

→ Change in postsynaptic through neuromodulation is by altering the response of postsynaptic cell.

* Postsynaptic receptor molecule:

① Ionotropic receptors:

→ Fast changes in membrane potential. (10^{-3} ms)

→ Ligand gated ion channel with binding site.

→ Ion channels

② Metabotropic receptors: (wide and diverse).

→ slow changes (100ms - 1s)

→ induce changes in electrical and biochemical properties.

→ Not ion channels

* Metabotropic receptors)

most metabotropic receptors belong to a important family of receptors called G protein coupled receptor or GPCR's

10-1. of all genes in human genome, all code for GPCR, there are around (over) 2,000 GPCR genes in human genome.

GPCR is a transmembrane protein complex

G proteins bind molecules guanosine triphosphate or (GTP). GTP is one of the 4 building blocks of DNA. GTP like its cousin ATP (adenosine triphosphate) plays a variety of different roles in the cell including serving as the raw material for DNA and RNA synthesis and acting as an energy storage molecule.

When the ligand binds to the GPCR, the alpha subunit can break free from beta and gamma subunits, and it can in turn interact with other proteins activating or inactivating them.

Ligand binding can cause a variety of effect within the cell, including the generation of other signalling molecules.

* Serotonin - neurotransmitter :-

→ Major neuromodulatory system of our brain involved in hunger, sleep and mood.

→ It is released in particular part of the brain called dorsal raphe nucleus.

→ Receptors are found in many parts of the brain. - hippocampus, midbrain, thalamus

amygdala as well as spinal cord

- Endogenous : substance produced by body.
Exogenous : opposite.

- * \rightarrow exclusive with bPCR's
- Neuropeptide (Neuromodulator) = peptide.
 - \hookrightarrow 5 - 20 amino acids in length.
 - Hypocretin - regulates sleep
 - Leptin - involved in appetite
 - Substance P - modulates pain

- Opioids (class of peptides) \rightarrow modulates pain perception

- * Dopamine - Neuromodulator

- \rightarrow produced by only 100,000 cells in brain.
- \rightarrow Projections are all over the entire brain.

Dopamine neurons originating in the substantia nigra are involved in regulating movement.

- Cocaine blocks the reuptake of dopamine from synaptic cleft : more time in synaptic cleft and increasing the likelihood of inserting a post-synaptic action.

- Acetylcholine is a neurotransmitter in the peripheral nervous system, as well as neuromodulator in central nervous system (CNS).

- * Drugs and interaction with their target receptors

- ① Agonist: Binds target receptor + has same effect as its normal ligand (generally activating the receptor).

- ② Antagonist: Binds target receptor + prevents from responding to the normal ligand i.e. prevents signal activation.

(3) Competitive: Binds to ligand binding site on a receptor + prevents the ligand from binding unless there is sufficient amount of ligand present so it can outcompete the drug.

(4) Nonspecific: Binds to a receptor at different location than the ligand binding site and modify the receptor in a way that prevents it from binding to the ligand.

* Noradrenaline / norepinephrine \rightarrow Neuromodulator.
 \rightarrow 1500 noradrenaline secreting neurons.

* Neuronal plasticity: Ability of neuronal circuits to change in response to numerous internal and external stimuli.

Classifications:

(1) Short term plasticity (2) Long term plasticity

(1) Short term plasticity:

\rightarrow milliseconds to minute.

\rightarrow (1) Short term strengthening of synaptic connection known as synaptic enhancement.

\rightarrow \uparrow presynaptic neurotransmitter \Rightarrow \uparrow presynaptic potential. \Rightarrow \uparrow excitatory post-synaptic potential (synaptic facilitation).

\rightarrow (2) short term weakening of synaptic connection (synaptic fatigue) - depletion of readily releasable neurotransmitter vesicles in pre-synaptic neuron upon repeated firing.

Also arise from post-synaptic neuron and feedback activation of pre-synaptic receptors.

② Long-term plasticity:

- Long term potentiation (LTP).
- Long term depression (LTD).

* Hebb's rule / Hebbian theory / Hebb's postulate / all assembly theory:

"Cells that fire together, wire together"
"Neurons out of sync lose their link".

* To make synapse stronger:

- ↑ neurotransmitter released
- ↑ postsynaptic receptors
- Post^{ts}synaptic receptor having larger effect.

* LTP classification: (due to molecular and structural change in synapse).

- a. Hebbian LTP
- b. Non-Hebbian LTP.
↳ classic form

Anti-Hebbian LTP:

- works in opposite direction to Hebbian LTP.
- occurs when pre and post synaptic neurons fire together.
- relaxing synapses.

* Long term depression (LTD) - weakening synapses

- LTD in the cerebellum results from strong synaptic stimulation
- Hippocampal LTD is induced by persistent weak synaptic stimulation
- In both the hippocampus and cerebellum, LTD is due to a decrease in receptor density.

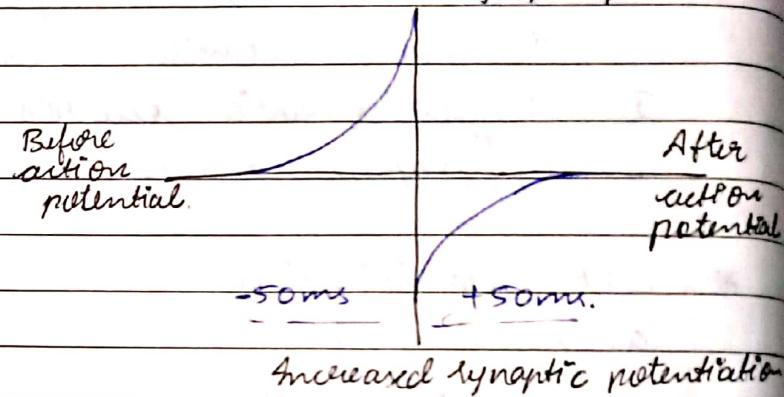
LTD occurs due to,

- Degradation of postsynaptic receptors and decrease in receptor density.
- Deactivation of AMPA receptor is shedding off phosphate group.

- * Spike timing-dependent plasticity (STDP)
 - ↳ definition of Hebbian plasticity is now here

"Presynaptic spikes arriving just a few tens of milliseconds before the postsynaptic spike result in potentiation, whereas presynaptic spikes arriving just after (few milliseconds) postsynaptic spike result in depression of the synapse."

"Presynaptic spikes arriving just after (few milliseconds) postsynaptic spike result in depression of the synapse"
increased synaptic potentiation



* Non-synaptic plasticity:

- They can occur in the soma, axons and dendrites of a neuron and typically involve modification of ion channel function at these sites.
- Since these functional changes are not locally restricted to synapses, the overall integration of excitatory and inhibitory postsynaptic potentials, and consequently its intrinsic excitability, are affected.
- These mechanisms keep the excitability of the neuron with some desirable range and are sometimes called "homeostatic" mechanisms.

Revising:

- Glutamate - main excitatory neurotransmitter in the central nervous system.
- Vesicles store neurotransmitter and its release to synaptic cleft is managed by V-SNARE
- Synaptic integration: Neurons combine information from many synapses at once.

① *

Synaptic distance from the cell body,

→ In the periphery, neuronal processes become smaller and thinner in diameter.

→ In a thinner neuron → axial resistance ↑ ⇒ conduction velocity ↓.

→ Peripheral dendrite not myelinated ⇒ signal attenuates much faster.

* 5 factors that regulate the interaction of synaptic inputs and their ability to initiate action potential in a target neuron:

① Synaptic efficacy and distance.

② Synaptic summation.

③ Synaptic inhibition.

④ Synaptic temporal summation.

⑤ Synaptic temporal inhibition.

② Synaptic summation: "Firing of 2 presynaptic neurons is integrated at the soma of the postsynaptic cell."

→ Action potential can also back propagate.

→ Dendrites can also generate spikes (new).

③ Synaptic inhibition: when both excitatory and inhibitory are activated, inhibitory neuron holds the membrane potential at around its resting potential and it effectively cancels out the EPSP.

This effect is called shunting.

- ④ Synaptic temporal summation: when synapse fires multiple times in succession, amplitude of EPSP is larger and different shape compared to the EPSP after a single activation.
→ Fast rise and slow fall of the EPSP caused by the state of 'openness' of a neuron's ligand-gated ion channels.
- ⑤ Synaptic temporal inhibition: Here membrane potential of the post-synaptic neuron returns to resting potential more quickly making the temporal summation less likely.
→ Metabotropic receptor: Few proteins that are bound to the receptor (G protein) can exert large amplified effect inside the cell.
⇒ NMDA require 2 ligands to open it, both glutamate and glycine must bind together
⇒ Synapse are the basis for memory and learning (meaning this is where memory is stored).
* Synapse allow learning in the brain through a mechanism called Habits Plasticity -
"If neuron A repeatedly takes part in firing neuron B, then the synapse from A to B is strengthened".
Bigger synapse \Rightarrow Good memory / learning.
 \hookrightarrow bigger the EPSP
Ex for Habit plasticity is LTP
evidence for synaptic strength - Habit plasticity
→ LTP/LTD depends on relative timing of I/p and

* Types of neuron:

- ① Sensory: carry information from sensory receptor cells throughout the body to brain
- ② Motor neurons: transmit information from the brain to the muscles of the body.
- ③ Interneurons: responsible for communicating info b/w different neurons in the body.