NEUROTRANSMITTER IN THE CNS

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B-Pharm 4th Semester Pharmacology-I

NEUROTRANSMITTER

- Neurotransmitters are endogenous chemical messengers that transmit signals from a neuron to a target cell across a synapse that enable neurotransmission.

NEUROMODULATOR

- Some chemicals released by neurons have little or no direct effects on their own but can modify the effects of neurotransmitters. These chemicals are called neuromodulators.
- Neurotransmitters and neuromodulators can be divided into two major categories
    1. Small-molecule transmitters
    2. Large-molecule transmitters.

Small-molecule transmitters

- Monoamines (e.g. acetylcholine, serotonin, histamine), catecholamines (dopamine, norepinephrine, and epinephrine), and amino acids (e.g. glutamate, GABA, glycine).

Large-molecule transmitters

- It includes Large number of peptides (short chains of amino acids linked by peptide bonds) called neuropeptides including substance P, enkephalin, vasopressin, and a host of others. In general, neuropeptides are co-localized with one of the small-molecule neurotransmitters.

CELL SIGNALING AND SYNAPTIC TRANSMISSION

Neurotransmitter synthesis

- Small-molecule neurotransmitters are synthesized in nerve terminals and peptides are synthesized in cell bodies and transported to nerve terminals.

Neurotransmitter storage

- The synthesized neurotransmitter are stored in the vesicle.

Neurotransmitter release

- Release of stored transmitter from the storage vesicle into the synaptic cleft occurs by exocytosis. Depolarization of the presynaptic neuron initiate the release process. The release based on Ca^{2+}-dependent release of vesicular contents.

Neurotransmitter recognition

- Neurotransmitters diffuse from sites of release and bind selectively to receptor proteins to initiate intracellular signal transduction within the postsynaptic cell.

Termination of action

- Mechanisms such as enzymatic inactivation, reuptake terminates the action.

CENTRAL NEUROTRANSMITTERS

- Chemically it is classified into amino acids, acetylcholine (ACh), monoamines, neuropeptides, purines, lipids, and gases.

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- Gamma-Aminobutyric Acid (GABA) (inhibitory neurotransmitter), Glycine (inhibitory neurotransmitter), Glutamate and aspartate (excitatory neurotransmitter) all three compounds are present in high concentrations in the CNS and are extremely potent modifiers of neuronal excitability.

GAMA-AMINO BUTYRIC ACID (GABA)

- GABA is the main inhibitory neurotransmitter in the CNS.
- GABA is synthesized in the brain from the Krebs cycle.
- It is located in high concentration in the substantia nigra and Globus pallidus nuclei of the basal ganglia, the hypothalamus, the periaqueductal grey matter, and the hippocampus.
- The concentration of GABA with in the brain is 200-1000 times greater than that of the monoamine or acetylcholine.
- Glutamate convert GABA by the enzyme glutamate decarboxylase.
- It consist of $GABA_A$ and $GABA_B$ receptor.

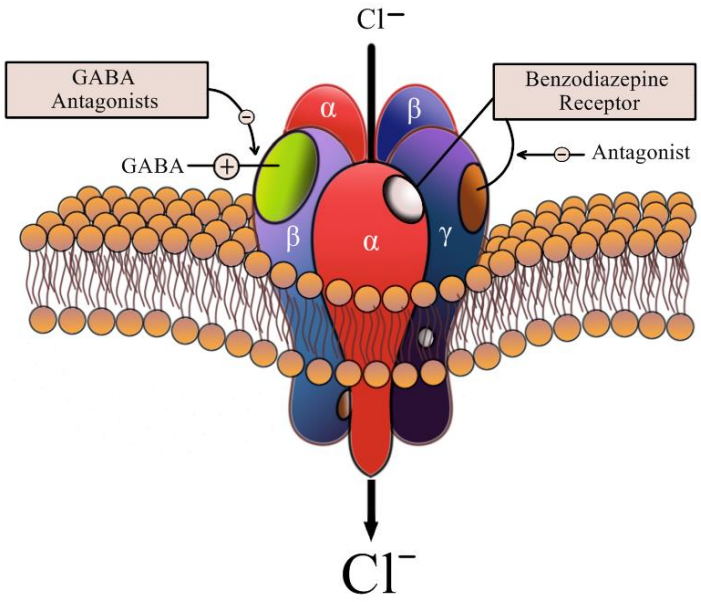

Figure 01: GABA receptor

$GABA_A$

- $GABA_A$ receptors are the most prominent GABA receptor subtype.
- They are made up of pentamers with different subunit such as α1-6, β1-3, γ1-3, δ, ε, θ, π and ρ1-3.
- Lot of subunits are cloned but few most common subunits are exist like α, β, and γ.
- Each receptor contains two α, two β and one γ subunits are arranged.
- GABA binds at each of the interfaces between α and β subunits whereas benzodiazepine binds with α and γ subunits.
- $GABA_A$ receptors are located primarily at post synaptic membrane and ionotropic, ligand-gated Cl- channels.
- It hyperpolarized the cell that why Cl^- ion enter into the cell and reduce excitability.
- The $GABA_A$ receptors have been extensively characterized as important drug targets and are the site of action of many neuroactive drugs including benzodiazepines, barbiturates, ethanol, anesthetic steroids, and volatile anesthetics.

$GABA_B$

- The $GABA_B$ receptors are metabotropic (type of membrane receptor that initiates a number of metabolic steps to modulate cell activity) GPCRs.
- Coupled through G_i / G_o to inhibit voltage gated Ca^{2+} channels and to open K^+ channel so Adenylyl cyclase inhibited.
- Found in central nervous system as well as peripheral nervous system.
- Maintain the equilibrium potential of K^+.
- $GABA_B$ receptors are widespread in the CNS and regulate both pre and postsynaptic activity.

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- Presynaptic $GABA_B$ receptors function as auto receptors, inhibiting GABA release, and may play the same role on neurons releasing other transmitters.
- Drugs such as baclofen (skeletal muscle relaxant) and Gamma-hydroxybutyrate [GHB] (psychoactive drug; sometimes used to treat narcolepsy) are acting on $GABA_B$ receptors.
- Subtypes of $GABA_B$ receptors: $GABAB_1$, $GABAB_2$.

Table 01: summary of GABA neurotransmitter

	$GABA_A$			**$GABA_B$**
	Receptor site	**Modulatory site (Benzodiazepine)**	**Modulatory site (Other)**	
Endogenous agonists	GABA	-	Progesterone metabolites	GABA
Other agonists	Muscimol, Gaboxadol (partial agonist)	Diazepam	Barbiturates	Baclofen
Antagonists	Bicuculline, Gabazine	Flumazenil (inverse agonist)	-	2-hydroxy-saclofen CGP 35348 and others
Channel blocker	Picrotoxin			-
Mechanism	Ligand-gated chloride channel.			GPCR, inhibition of Ca^{2+} channels, activation of K^+ channels, inhibition of Adenylyl cyclase.
Location	Widespread; primarily postsynaptic			Pre and post synaptic membrane.
Function	Postsynaptic inhibition (Fast IPSP)			Presynaptic inhibition (decrease Ca^{2+} entry), postsynaptic inhibition (increased K^+ permeability)

GLYCINE

- It is also an inhibitory neurotransmitter, found mainly in the spinal cord, brain stem and retina.
- Only present in the vertebrates.
- It is a simple amino acid, released into the synaptic cleft, binds to the receptors and facilitate Cl^- ions.
- Glycine hyperpolarized the membrane.
- **Antagonist:** Strychnine – binds to the glycine receptor and prevent the opening of Cl^- ion channel.

GLUTAMATE AND ASPARTATE

- Glutamic acid is an excitatory transmitter in the central nervous system. Aspartate have also similar role in the certain brain region.
- Glutamate and related excitatory amino acids activate both ionotropic (ligand-gated cation channel) and metabotropic (G-protein coupled) receptors.

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IONOTROPIC GLUTAMATE RECEPTOR

- On the basis of agonists and antagonists there are three main sub types of glutamate ionotropic receptor;
    1. NMDA (N-methyl-D-aspartate receptor)
    2. AMPA (α-amino-3hydroxy-5-methyl-4-isoxazolepropionic acid receptor)
    3. Kainate receptor

NMDA

- NMDA receptors are assembled from seven types of subunit (GluN1, GluN2A, GluN2B, GluN2C, GluN2D, GluN3A, and GluN3B).
- The NMDA receptor is very important for controlling synaptic plasticity and memory function.
- They are highly permeable to Ca^{2+}, as well as to other cations.
- This channels are rapidly blocked by Mg^{2+}.
- Activation of NMDA receptors requires glycine as well as glutamate.
- The glycine binding site or glutamate binding site is distinct for each other.
- Glycine is an allosteric modulator.
- The activity of the NMDA receptor is affected by many psychoactive drugs such as phencyclidine (PCP), alcohol (ethanol), and dextromethorphan (DXM).
- The anaesthetic agent such as ketamine is selective blocking agent for NMDA operated channels.

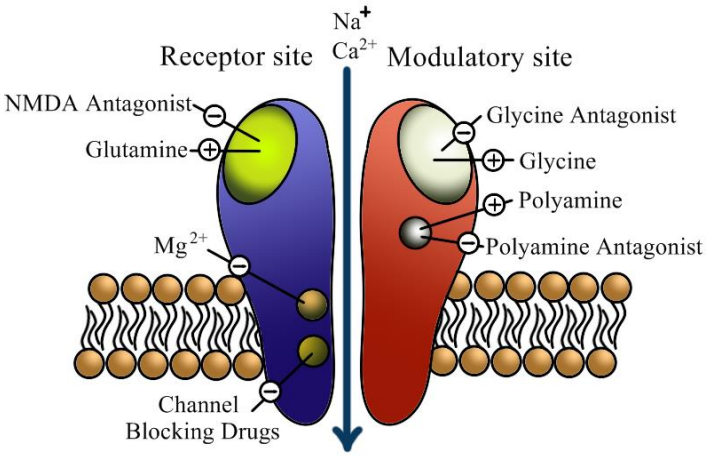

Figure 02: NMDA receptor

AMPA and Kainate

- AMPA and kainate receptors, serve to mediate fast excitatory synaptic transmission in the CNS.
- Fast excitation primarily associated with influx of Na^+ ion.
- AMPA receptors occur on astrocytes as well as on neurons, and these cells play an important role in communication in the brain.
- Agonist for AMPA and kainate are AMPA, Quisqualate and Kainate, Domoate.
- NBOX is a selective antagonist of AMPA and kainate.

Table 02: properties of ionotropic glutamate receptor

	NMDA		AMPA	Kainate
Subunits	Tetramers - GluN1–3		Tetramers - GluA1–4	Tetramers - GluK1–5
	Receptor site	**Modulatory site (glycine)**		
Endogenous agonists	Glutamate, Aspartate	Glycine, D-Serine	Glutamate	Glutamate

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Other agonists	NMDA	Cycloserine	AMPA, Quisqualate	Kainate, Domoate
Antagonists	AP5, CPP	7-Chloro kynurenic acid, HA-966	NBQX	NBQX, ACET
Modulators	Polyamines (e.g. spermine, spermidine) Mg^{2+}, Zn^{2+}		Cyclothiazide, Perampanel, Piracetam, CX-516	-
Channel blockers	Dizocilpine (MK801), Phencyclidine, ketamine, Remacemide, Memantine, Mg^{2+}		-	-
Mechanism	Ligand-gated cation channel (slow kinetics, high Ca^{2+}permeability)		Ligand-gated cation channel (fast kinetics; channels possessing GluA2 subunits show low Ca2+ permeability)	Ligand-gated cation channel (fast kinetics, low Ca^{2+} permeability)
Location	Postsynaptic (some presynaptic, also glial) Wide distribution		Postsynaptic (also glial)	Pre- and postsynaptic
Function	Slow EPSP, Synaptic plasticity (long-term potentiation, long-term depression). Excitotoxicity (toxic actions of excitatory neurotransmitters)		Fast EPSP, Wide distribution	Fast EPSP, Presynaptic inhibition, Limited distribution
Abbreviations	• **AP5:** 2-amino-5-phosphonopentanoic acid • **CPP:** 3-(2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid • **ACET:** -(S)-1-(2-amino-2-carboxyethyl)-3-(2-carboxy-5-phenylthiophene-3-yl-methyl)-5-methylpyrimidine-2,4-dione • **NBQX:** 2,3-dihydro-6-nitro-7-sulfamoyl-benzoquinoxaline • **CX-516:** 1-(quinoxalin-6-ylcarbonyl)-piperidine			

METABOTROPIC GLUTAMATE RECEPTORS

- There are eight different metabotropic glutamate receptors (mGlu1–8).
- mGlu receptors are widely distributed throughout the central nervous system.
- They regulate cell excitability and synaptic transmission, and on glia.
- Neuronal group 1 mGlu receptors are located postsynaptically and are largely excitatory, by raising intracellular [Ca^{2+}].
- Group 2 and 3 mGlu receptors are mostly presynaptic receptors and their activation tends to reduce synaptic transmission and neuronal excitability.
- They are also act as autoreceptor, involved in reducing glutamate release or heteroreceptors.

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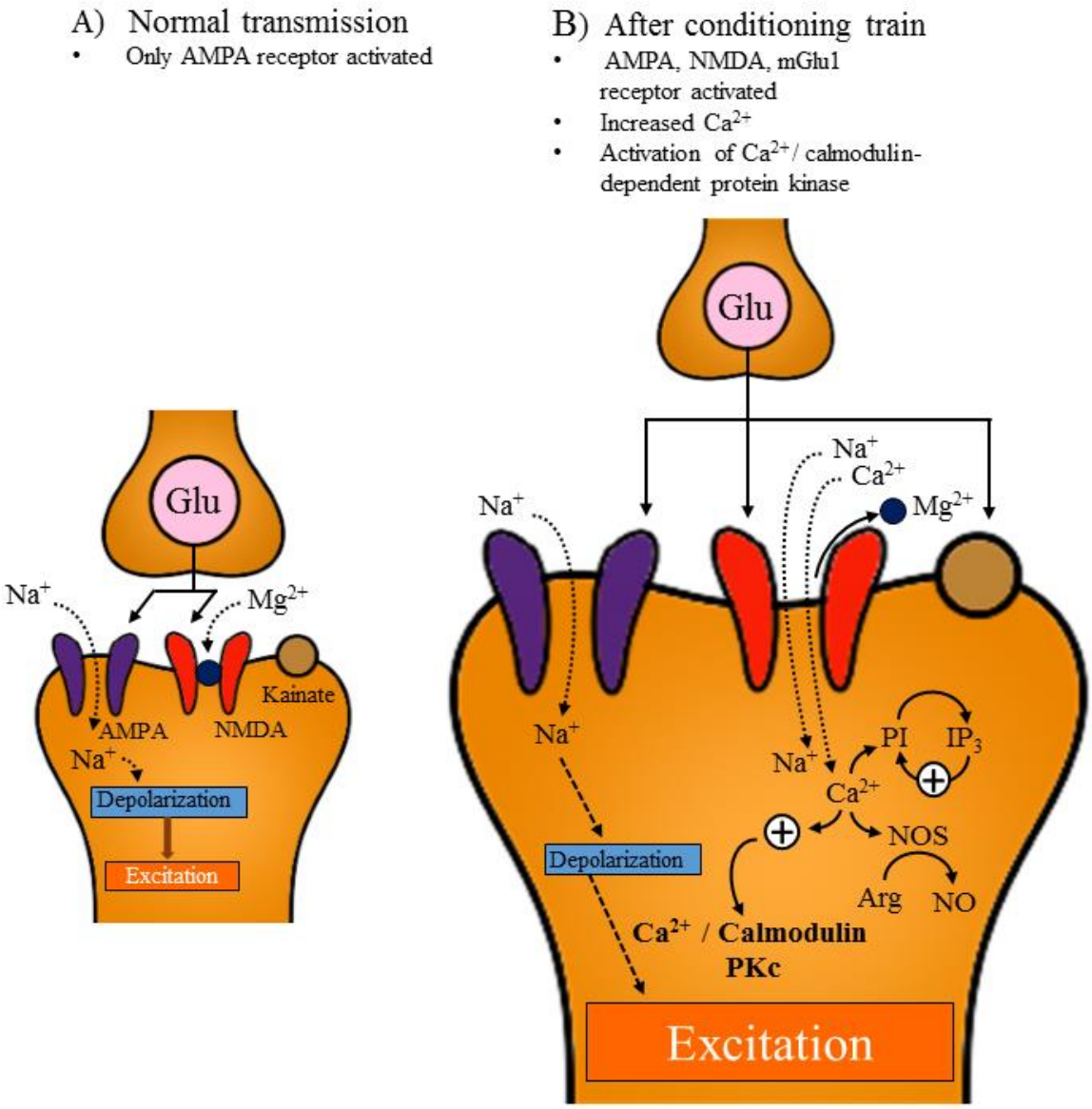

Figure 03: Glutamate transmission. A) Normal transmission and B) After conditioning train

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DOPAMINE

- Dopamine is a monoamine catecholamine.
- It is very important for the various neurological disorder of brain function, like Parkinson's disease, schizophrenia and attention deficit disorder, as well as in drug dependence and certain endocrine disorders.
- Dopamine is most abundant in the corpus striatum and high concentrations also occur in certain parts of the frontal cortex, limbic system and hypothalamus.

DOPAMINERGIC PATHWAYS IN THE CNS

- There are four main dopaminergic pathways in the brain.
    1. **Nigrostriatal pathway:** Substantia nigra (SNc) neurons project to the corpus striatum.
    2. **Mesolimbic pathway:** Ventral tegmental area (VTA) neurons project to the nucleus accumbens (NAc) and the amygdaloid nucleus (AC).
    3. **Mesocortical pathway:** VTA neurons project to the frontal cortex.
    4. **Tuberohypophyseal / Tuberoinfundibular:** a group of short neurons running from the ventral hypothalamus to the median eminence and pituitary gland, the secretions of which they regulate.

DOPAMINE TRANSMISSION

- Tyrosine is taken up in to the nerve terminals through the tyrosine transporter and it is converted into DOPA (Dihydroxyphenylalanine) by the enzyme tyrosine hydroxylase (TH).
- DOPA is then converted into the Dopamine by the help of enzyme DOPA decarboxylase (DDC).
- Dopamine is stored in the vesicle via vesicular monoamine transporter (VMAT2).
- During transmission Dopamine released to synaptic cleft and binds to its corresponding receptors like D_1 and D_2 etc.
- After binging to the receptor it shows adenylyl cyclase activation or inhibition.
- Excess release of dopamine at the synaptic cleft are reuptake in to presynaptic membrane through dopamine transporter (DAT).
- Dopamine is degraded by mainly two enzymes catechol O-methyl transferase (COMT) and monoamine oxidase (MAO).

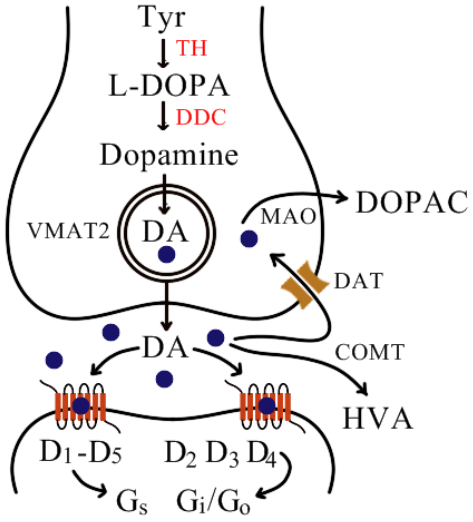

Figure 04: Dopamine transmission

- MAO is of two types MAO-A and MAO-B.
- MAO-A (deaminates serotonin and norepinephrine) and MAO-B (deaminates dopamine, histamine and broad spectrum of phenylethylamine).
- The metabolites of Dopamine are 3, 4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA).

DOPAMINE RECEPTORS

- There are two types of dopamine receptors D_1 and D_2. The sub families includes D_1 family D_1 and D_5, while D_2 family consists of D_2, D_3, and D_4.

- Location of dopamine receptors

D_1 family		D_2 family		
D_1	**D_5**	**D_2**	**D_3**	**D_4**
• Substantia nigra • Nucleus accumbens • Olfactory bulb • Cerebellum • Hippocampus • Thalamus • Kidney	• Substantia nigra • Hypothalamus • Kidney • Heart • Sympathetic ganglia	• Substantia nigra • Nucleus accumbens • Ventral tegmental area • Heart • Blood vessel • Adrenal glands • Sympathetic ganglia	• Olfactory bulb • Nucleus accumbens	• Heart • Blood vessels • Substantia nigra • Hippocampus • Amygdala • Gastrointestinal tract

- D_1 and D_5 receptors are stimulation of adenylyl cyclase.
- D_2, D_3, and D_4 receptors are linked to activation of K+ channels and inhibition of Ca2+ channels as well as to inhibition of adenylyl cyclase.

FUNCTIONS OF DOPAMINE

- Motor function
- **Behavioral effects: Amphetamine and cocaine** activate mesolimbic dopaminergic 'reward' pathways to produce feelings of euphoria in humans.
- **Neuroendocrine function:** Inhibit prolactin release. **Bromocriptine** (dopamine receptor agonist) used to suppress prolactin secretion. **Cabergoline** enhance libido and sexual performance.
- **Vomiting:** Dopamine acts on the chemoreceptor trigger zone to cause nausea and vomiting

SEROTONIN / 5-HYDROXYTRYPTAMINE (5-HT)

- 5-HT is a monoamine neurotransmitter.
- Biologically it is derived from tryptophan.
- Tryptophan is taken up into the neuron, converted to 5-hydroxytryptophan by tryptophan hydroxylase and decarboxylated by a non-specific amino acid decarboxylase to form 5-HT.
- 5-HT neurons are concentrated in the midline raphe nuclei in the brain stem projecting to the cortex, limbic system, hypothalamus and spinal cord.
- The main receptor subtypes in the CNS are 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{2A}, 5-HT_{2C}, and 5-HT_3. These receptors are associated of behavioral and physiological functions.
- Other receptor types 5-$HT_{4\text{-}7}$ also present in the CNS, but has less function known.
- Drugs acting selectively on 5-HT receptor or transporter includes: **Buspirone** (5-HT_{1A} agonist), **Sumatriptine** (5-HT_{1D} agonist), **Pizotifen** (5-HT_2 antagonist), **Fluoxetine** (SSRIs), **and Ondansetron** (5-HT_3 antagonist).
- Function associated with 5-HT includes: Hallucination, Control mood and emotion, Control of sleep/wakefulness, control body temperature, vomiting.

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