Introduction to CNS Drugs

- Cns drugs are among the first to be discovered by primitive humans
- Most widely used drugs to :-
- treat wide range of neurologic and psychiatric illnesses
- relieve pain
- Suppress nausea
- Reduce fever
- Increase the sense of wellbeing

- Cns drugs act on specific receptors that modulate synaptic transmission except general anesthetics and alcohol which have non specific action on membranes.
- These drugs are valuable tools for studying cns function
- They help in understanding pathophysiology of disease e.g. Schizophrenia.

Organisations of CNS

- Cns is composed of brain and spinal cord
- Neurons;human brain contains hundred billion neurons,these are electrically excitable cells that process and transmitt information via electro chemical process.
- Neurons are present as clusters i.e.nuclei
- OR they are present as layered structures i.e. Cerebellum and hippocampus
- Neuroglia;non neuronal support cells such as astrocytes,oligodentrocytes and microglia

CONTD

- Blood brain barrier:it is a protective functional separation of the circulatoing blood from extracellular fluid of CNS that limits the penetration of drug into the cns.
- Hydrophilic drugs can cross this barrier or else a specific transport system is required

Functions of CNS

- It is the master controlling and communicating system of the body
- It controls and coordinates all essential functions of the human body
- Sensory function;millions of sensory receptors are used to monitor changes occurring both inside and outside the body.(sensory input)
- Integrative function:nervous system processes and interprets sensory input
- Motor function;nervous system sends signals to muscles,glands and organs for an appropriate response

Neurotransmission by action potential

- Nerve signals are transmitted by action potential that are abrupt pulse like changes in membrane potential
- Action potential is divided into 3 phases:

1. Resting phase
2. Depolarisation phase
3. Repolarisation phase

- Excitatory postsynaptic potentials and inhibitory post synaptic potentials are inputs that depolarize/hyperpolarize the postsynaptic cell bringing it closer/away from firing an action potential.
- EPSP are caused by opening of channels that are permeable to Na and K
- Neurotransmitters:Ach,dopamine,serotonin
- IPSP are caused by opening of chloride channels
- Neurotransmitters:GABA and Glycine

Neurotransmitters

- Acetylcholine
- Serotonin
- Norepinephrine
- Dopamine
- GABA
- Glutamate
- Most drugs that affect CNS act by altering some step in the neurotransmitters mediating the physiological and pathological response in neuropharmacology

Acetylcholine

- Myasthenia gravis is characterized by skeletal muscle weakness and fatigability resulting from reduced number if Ach receptors on muscle end plate(due to autoimmune antibodies against Ach receptors at neuromuscular junction).
- Diagnosis and treatment involves Acetylcholinestrase inhibitors (neostigmine)that prolongs the action of Ach at muscle end plate
- Ach esterase inhibitors (Tacrine)-Alzhimers Disease
- Anticholinergics(Benztropine)in Parkinson's Disease

Serotonin

- Involved in mood,depression and pain regulation.
- Activities modified by :
- Antidepressants
- CNS stimulants

Dopamine

- Involved in movement,attention,learning,motivation and reward
- Overactive dopamine:
- Schizophrenia (antipsychotics)
- Loss of dopamine :
- Parkinson's Disease(Levodopa)

GABA

- Main inhibitory neurotransmitter in CNS
- Anxiety disorders(Benzodiazepines)
- Huntingtons chorea that involve loss of neurons that utilize GABA.

Glutamate

- High concentration of glutamate lead to neuronal cell death by mechanisms that have only recently begun to be clarified.The cascade of events leading to neuronal death is thought to be triggered by excessive activation of NMDA or AMPA/kinase receptors allowing significant influx of calcium into neurons
- Due to their widespread distribution in CNS,gluatamte receptors have become target for diverse therapeutic interventions. For example,a role for disordered glutamatergic transmission in the etiolgy of chronic neurodegenerative diseases and in schizophrenia has been postulated

TABLE 21–2 Summary of neurotransmitter pharmacology in the central nervous system.

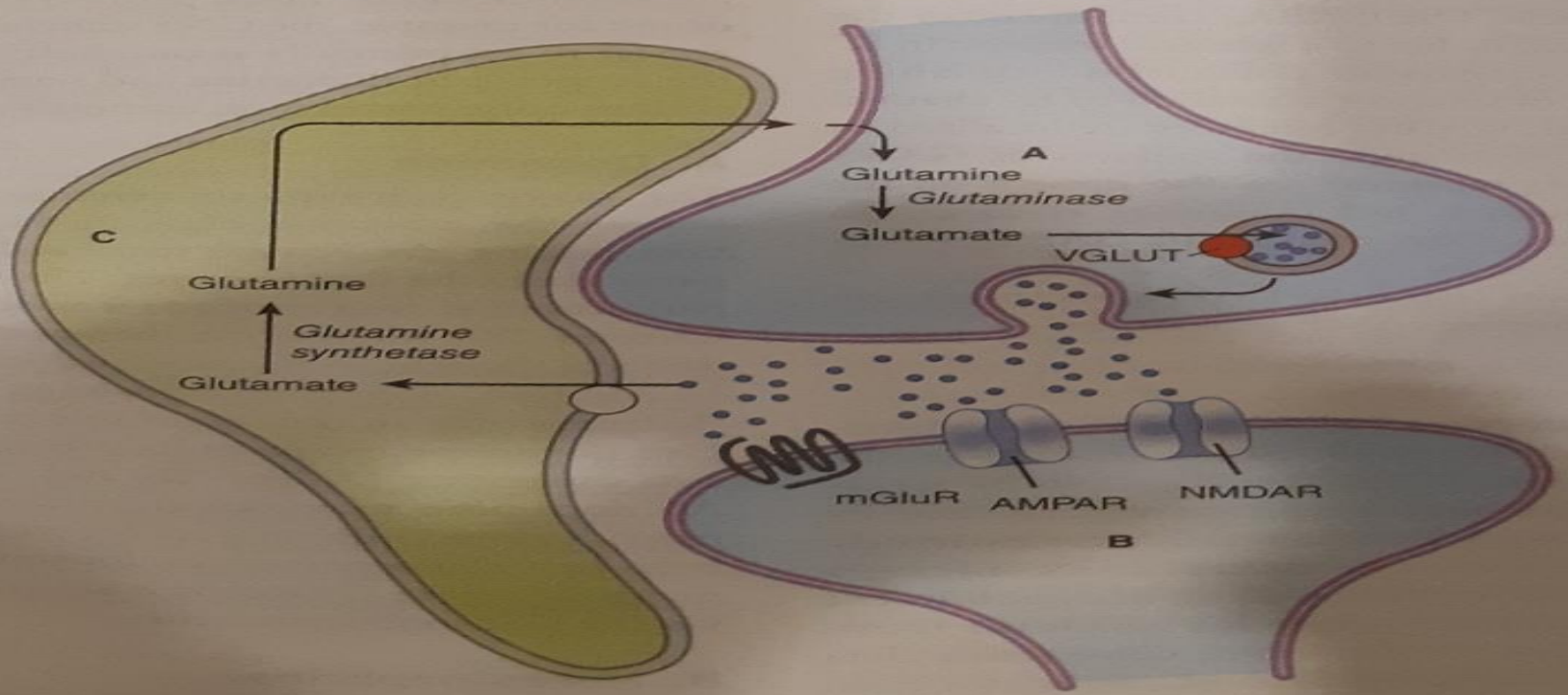
Transmitter	Anatomy	Receptor Subtypes and Preferred Agonists	Receptor Antagonists	Mechanisms
Acetylcholine	Cell bodies at all levels; long and short connections	Muscarinic (M_1): muscarine	Pirenzepine, atropine	Excitatory: ↓ in K^+ conductance; ↑ IP_3, DAG
		Muscarinic (M_2): muscarine, bethanechol	Atropine, methoctramine	Inhibitory: ↑ K^+ conductance; ↓ cAMP
	Motoneuron-Renshaw cell synapse	Nicotinic: nicotine	Dihydro-β-erythroidine, α-bungarotoxin	Excitatory: ↑ cation conductance
Dopamine	Cell bodies at all levels; short, medium, and long connections	D_1: dihydrexidine	Phenothiazines	Inhibitory (?): ↑ cAMP
		D_2: bromocriptine	Phenothiazines, butyrophenones	Inhibitory (presynaptic): ↓ Ca^{2+}; Inhibitory (postsynaptic): ↑ in K^+ conductance, ↓ cAMP
GABA	Supraspinal and spinal interneurons involved in pre- and postsynaptic inhibition	$GABA_A$: muscimol	Bicuculline, picrotoxin	Inhibitory: ↑ Cl^- conductance
		$GABA_B$: baclofen	2-OH saclofen	Inhibitory (presynaptic): ↓ Ca^{2+} conductance; Inhibitory (postsynaptic): ↑ K^+ conductance
Glutamate	Relay neurons at all levels and some interneurons	*N*-Methyl-D-aspartate (NMDA): NMDA	2-Amino-5-phosphonovalerate, dizocilpine	Excitatory: ↑ cation conductance, particularly Ca^{2+}
		AMPA: AMPA	NBQX	Excitatory: ↑ cation conductance
		Kainate: kainic acid, domoic acid	ACET	Excitatory: ↑ cation conductance
		Metabotropic: ACPD, quisqualate	MCPG	Inhibitory (presynaptic): ↓ Ca^{2+} conductance, ↓ cAMP; Excitatory: ↓ K^+ conductance, ↑ IP_3, DAG
Glycine	Spinal interneurons and some brain stem interneurons	Taurine, β-alanine	Strychnine	Inhibitory: ↑ Cl^- conductance
5-Hydroxytryptamine (serotonin)	Cell bodies in mid-brain and pons project to all levels	$5\text{-}HT_{1A}$: eptapirone	Metergoline, spiperone	Inhibitory: ↑ K^+ conductance, ↓ cAMP
		$5\text{-}HT_{2A}$: LSD	Ketanserin	Excitatory: ↓ K^+ conductance, ↑ IP_3, DAG
		$5\text{-}HT_3$: 2-methyl-5-HT	Ondansetron	Excitatory: ↑ cation conductance
		$5\text{-}HT_4$: cisapride	Piboserod	Excitatory: ↓ K^+ conductance
Norepinephrine	Cell bodies in pons and brain stem project to all levels	α_1: phenylephrine	Prazosin	Excitatory: ↓ K^+ conductance, ↑ IP_3, DAG
		α_2: clonidine	Yohimbine	Inhibitory (presynaptic): ↓ Ca^{2+} conductance; Inhibitory: ↑ K^+ conductance, ↓ cAMP
		β_1: isoproterenol, dobutamine	Atenolol, practolol	Excitatory: ↓ K^+ conductance, ↑ cAMP
		β_2: albuterol	Butoxamine	Inhibitory: may involve ↑ in electrogenic sodium pump; ↑ cAMP
Histamine	Cells in ventral posterior hypothalamus	H_1: 2(*m*-fluorophenyl)-histamine	Mepyramine	Excitatory: ↓ K^+ conductance, ↑ IP_3, DAG
		H_2: dimaprit	Ranitidine	Excitatory: ↓ K^+ conductance, ↑ cAMP
		H_3: *R*-α-methyl-histamine	Thioperamide	Inhibitory autoreceptors

(continued)

r	Anatomy	and Preferred Agonists	Receptor Antagonists	Mechanisms
ides	Cell bodies at all levels; long and short connections	Mu: bendorphin	Naloxone	Inhibitory (presynaptic): ↓ Ca^{2+} conductance, ↓ cAMP
		Delta: enkephalin	Naloxone	Inhibitory (postsynaptic): ↑ K^+ conductance, ↓ cAMP
		Kappa: dynorphin, salvinorin A	Naloxone	Inhibitory (postsynaptic): ↑ K^+ conductance, ↓ cAMP
	Cell bodies in hypothalamus; project widely	OX_1: orexin A	Suvorexant	Excitatory, glutamate co-release
		OX_2: orexins A and B	Suvorexant	
	Primary sensory neurons, cell bodies at all levels; long and short connections	NK1: substance P methylester	Aprepitant	Excitatory: ↓ K^+ conductance, ↑ IP_3, DAG
		NK2: neurokinin A	Saredutant	Excitatory: ↓ K^+ conductance, ↑ IP_3, DAG
		NK3: neurokinin B	Osanetant	Excitatory: ↓ K^+ conductance, ↑ IP_3, DAG
noids	Widely distributed	CB1: anandamide, 2-arachidonyglycerol	Rimonabant	Inhibitory (presynaptic): ↓ Ca^{2+} conductance, ↓ cAMP

central transmitters have been identified (see text).

ino-2-carboxyethyl)-3-(2-carboxy-5-phenylthiophene-3-yl-methyl)-5-methylpyrimidine-2,4-dione; ACPD, *trans*-1-amino-cyclopentyl-1,3-dicarboxylate; AMPA, droxy-5-methylisoxazole-4-propionate; cAMP, cyclic adenosine monophosphate; DAG, diacylglycerol; IP_3, inositol trisphosphate; LSD, lysergic acid diethylamide; 4-carboxyphenylglycine; NBQX, 2,3-dihydroxy-6-nitro-7-sulfamoylbenzo(*f*)quinoxaline.



7 Schematic diagram of a glutamate synapse. Glutamine is imported into the glutamatergic neuron **(A)** and converted into taminase. The glutamate is