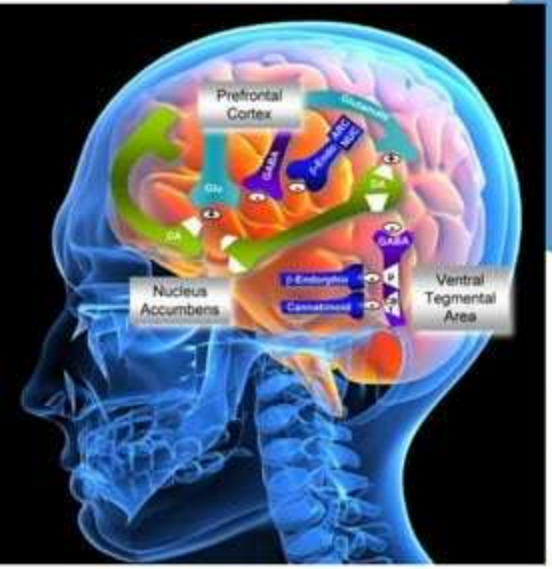
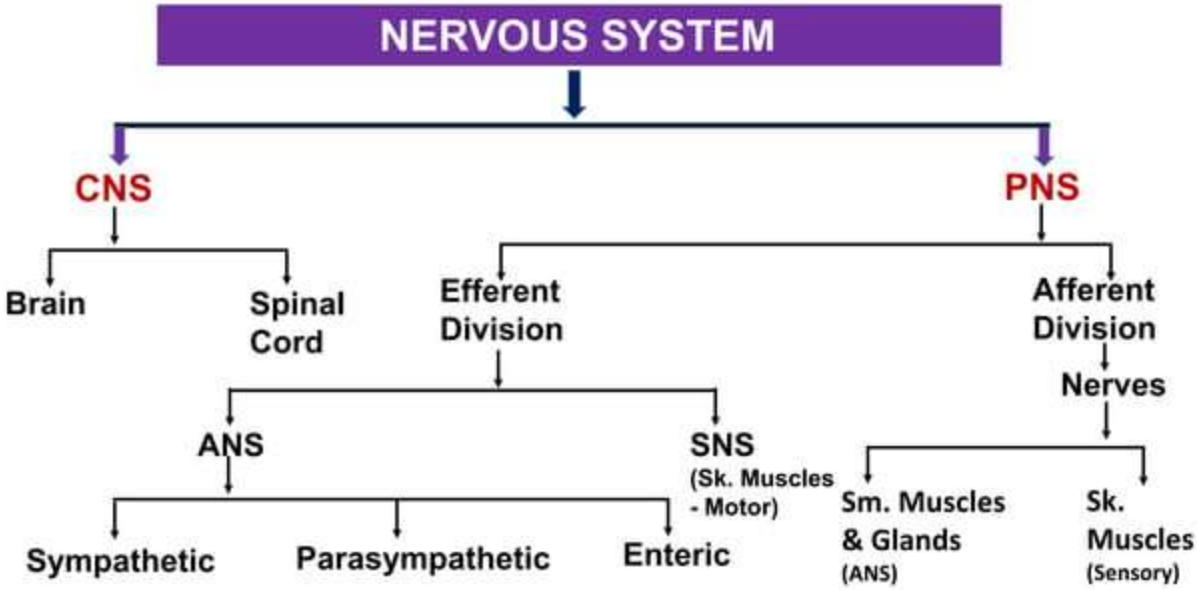


Pharmacology of Nervous System

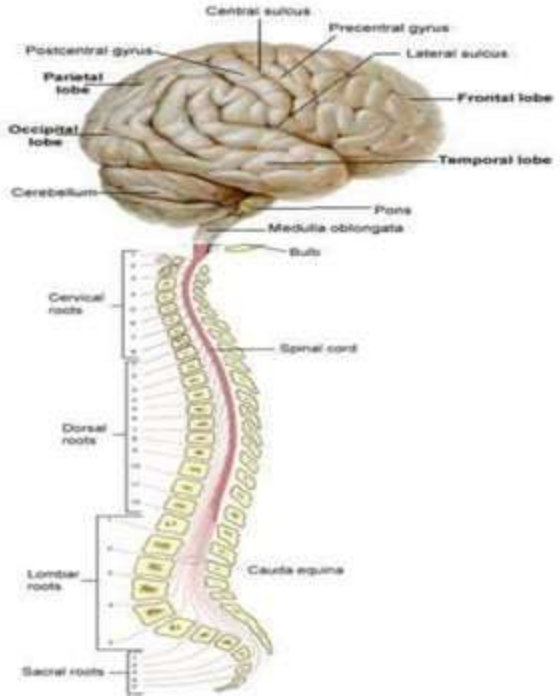
Learn anatomy and physiology here

Talk Plan

- Classification
- Definitions
- Neurotransmitters
- Drugs acting on CNS
- CNS depressants
- CNS stimulants
- Miscellaneous
- Drugs acting on PNS
- Sympathetic NS
- Parasympathetic NS
- Adrenergic drugs
- Antiadrenergic drugs
- Cholinergic drugs
- Anticholinergic drugs


NERVOUS SYSTEM
CNS
PNS
Brain
Spinal Cord
Efferent Division
Afferent Division
Nerves
ANS
SNS
(Sk. Muscles - Motor)
Sympathetic
Parasympathetic
Enteric
Sm. Muscles & Glands
(ANS)
Sk. Muscles
(Sensory)

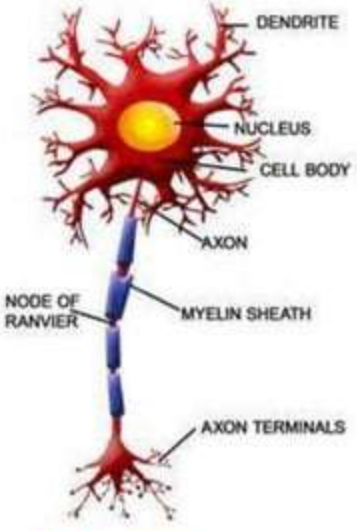
CNS Pharmacology



Neurons: Structural & Functional Unit of NS (10 billion neurons in brain)

Neuro-transmitters:

- Chemical substances
- Carry messages from one neuron to another
- or from a neuron to body tissues e.g. Sk. muscles



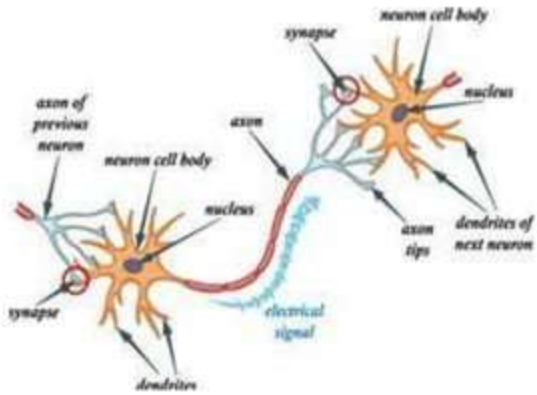
A Neuron

Synapse:

Small gap separating neurons

Receptors:

- Macro-molecules
- Lipoprotein in nature
- Situated on or inside the cell membrane
- Having recognition properties



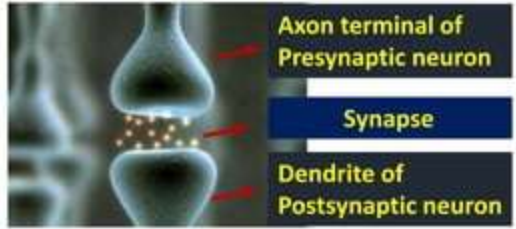


Fig: Synapse

Process of Typical Synaptic Connection

Presynaptic membrane or element

↓

Action Potential

↓

Activates Ca^{++} ion Channel

↓

Neurotransmitters

↓

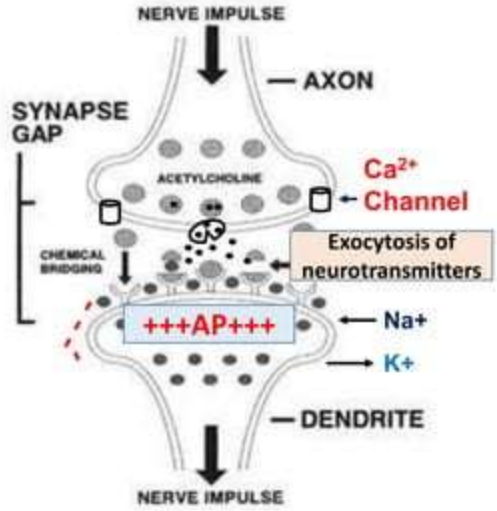
Released in Synaptic Cleft

↓

Post synaptic membrane (receptors or ion channels)

↓

Exert action



Neurotransmitters in CNS

I. Amino acids : Ach, GABA, Glutamate, Glycine

II. Monoamines : NE, Dopamine, Serotonin

III. Peptides : Opioid peptides, Neurotensin, Substance P, Somatostatin, Neuropeptide Y

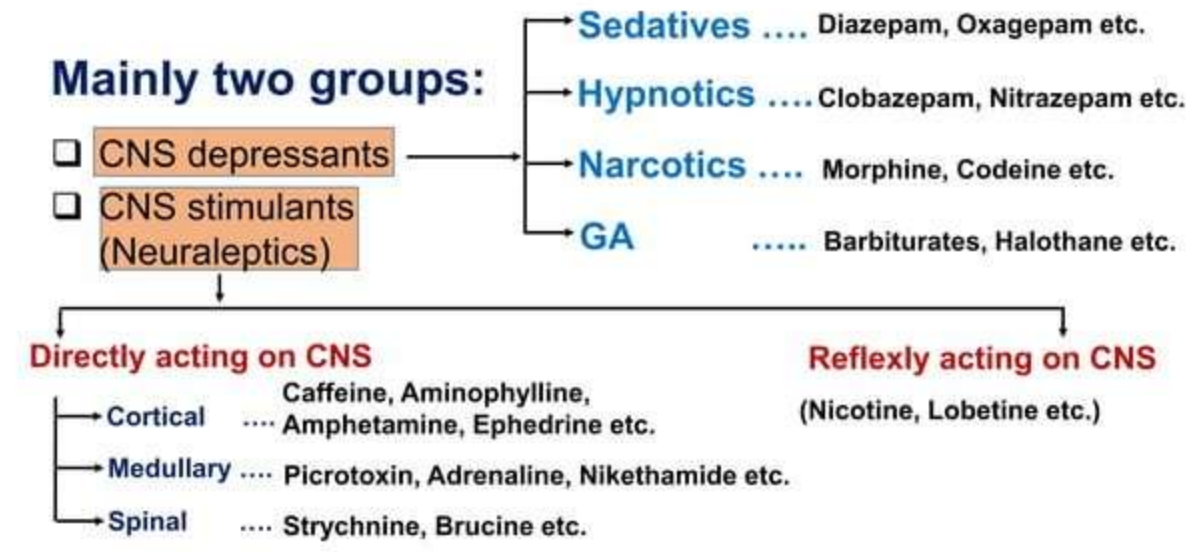
IV. Nitric oxide

V. Endocannabinoids

VI. Histamine

VII. Tachykinins

Drugs acting on CNS



Drugs acting on CNS

CNS Depressants: Anxiolytics and Sedative-Hypnotics

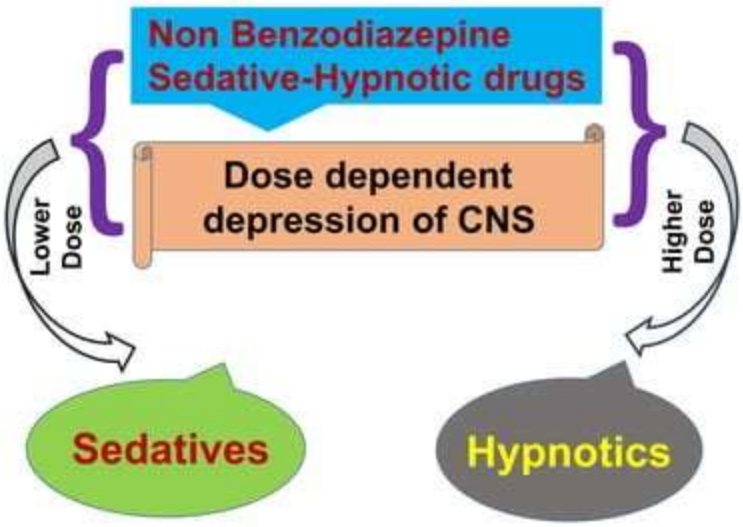
Sedatives (anxiolytic):

- Anxiolytic drug
- Reduce anxiety, excitement, nervousness, irritability
- Exert calming effect
- Mild depression of CNS
- Don't cause sleep
- Little or no effect on motor or mental functions

Hypnotics:

Depress CNS to the point that they cause normal sleep

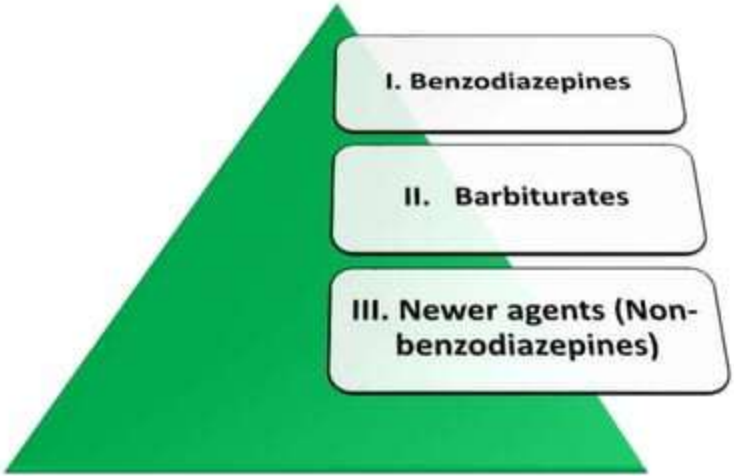
CNS Depressants: Anxiolytics and Sedative-Hypnotics



Progressive Depression of CNS

Sedation
⇩
Hypnosis
⇩
Narcosis
⇩
Coma
⇩
GA
⇩
Death

Classification: Sedatives-Hypnotics



Sedatives-Hypnotics: Benzodiazepines

- Benzene ring fused to seven membered diazepine ring
- Frequently prescribed
- Favourable side effect
- Efficacy, safety

Classification

a) **Short acting ($t_{1/2}$ < 5 hrs)**
   Midazolam, Triazolam etc.

b) **Intermediate acting ($t_{1/2}$ 8-40 hrs)**
   Lorazepam, Temazepam etc.

c) **Long acting ($t_{1/2}$ 40-250 hrs)**
   Diazepam, Nitrazepam etc.

MOA of Benzodiazepines

Benzodiazepines

↓

Binds with specific regulatory site on GABA receptor in brain

↓

Enhance GABA activity

↓

↓

Opening of Cl- channels (Enhancement of Cl- conductance)

↓

Hyperpolarization of cells

↓

Depression of CNS

Pharmacological action: Benzodiazepines

CNS effects:

- Anxiolytic
- Sedation & induction of sleep
- Muscle relaxation (skeletal)
- Anticonvulsant effects
- Anterograde amnesia
- Decrease dose of anaesthetic

Peripheral action:

- Neuromuscular blockade (high dose)
- Coronary vasodilation (IV)

Adverse effects & Choice: Benzodiazepines

Adverse effects

a) Normal dose:
- **Dry mouth**
- **Light headache**
- **Confusion**
- **Ataxia**
- **Impair driving skill**

b) Acute overdose: Prolong sleep

c) Tolerance & dependency

d) Decrease libido

Sedatives-Hypnotics: Barbiturates

Malonic acid

↓

Barbituric acid

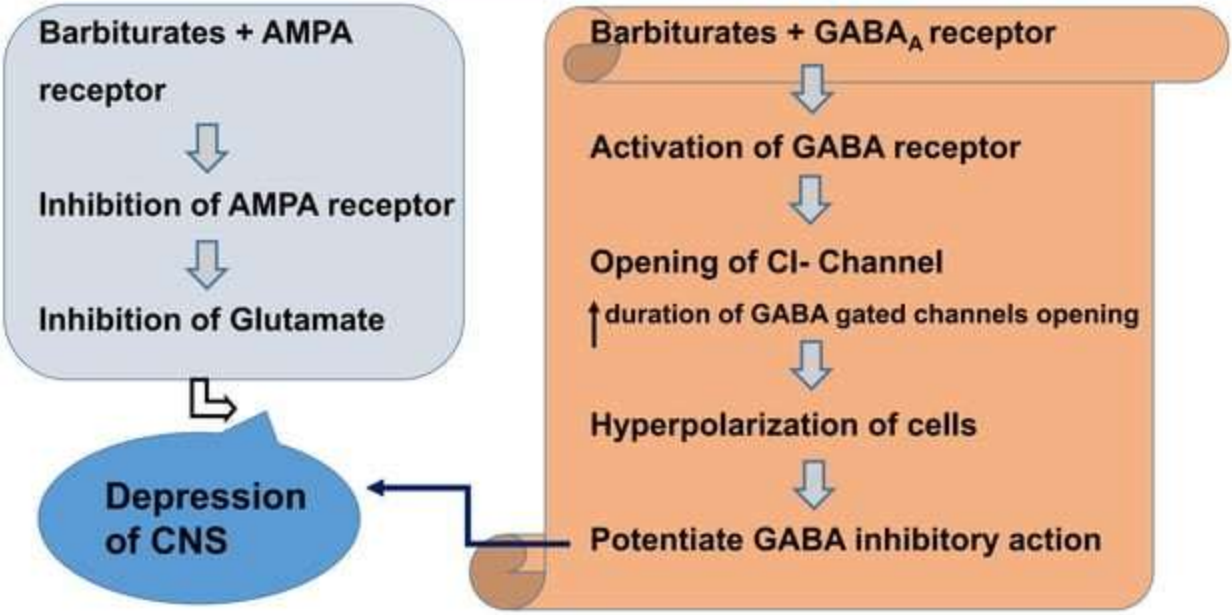
↓

Barbiturates

Classificatin

Ultra-short acting (e.g. Thiopental-Na)	• Acts within seconds, DOA: 30 mins • Main use: IV anaesthetic
Short acting (e.g. Pentobarbital)	• DOA: 2 hours • Main use: Sedative
Intermediate acting (e.g. Amobarbital)	• DOA: 3-5 hours • Main use: Hypnotic
Long acting (Phenobarbitone)	▪ DOA: > 6 hours ▪ Main use: Anticonvulsant

Barbiturates: MOA



Barbiturates: Indications & Adverse effects

Indications

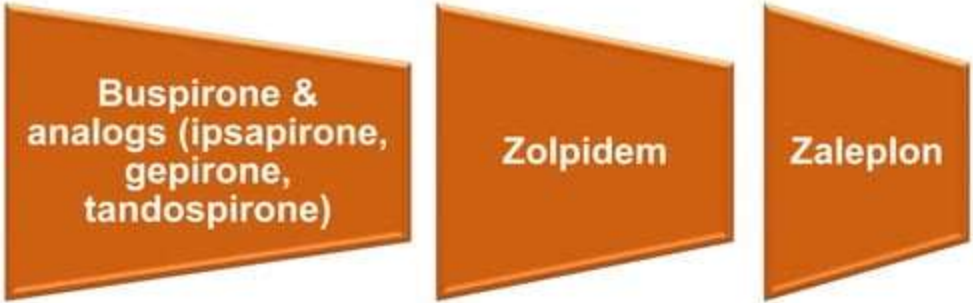
- Anticonvulsants
- Sedative & Hypnotics
- IV anesthesia
- Hyperbilirubinemia
- Kernicterous
- Cholestasis

Adverse effects

- Drowsiness
- Over excitement
- Night mares & night terrors
- Weakness
- Allergic skin reaction
- Localized or diffuse pain
- Psychologic dependence
- Tolerance

Sedatives-Hypnotics: Newer drugs

Anxiety & Sleep Disorder



CNS Depressants: Tranquilizers

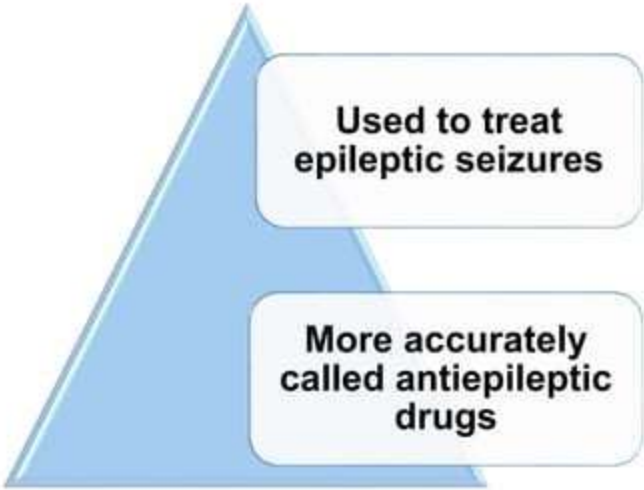
- Produce calmness & quietness
- Reduce anxiety, tension & aggression
- Also called “PEACE PILL”

Example:

Major: Phenothiazine derivatives (Chlorpromazine, Promethazine etc.), Reserpine etc.

Minor: Benzodiazepines, Phenobarbitone etc

CNS Depressants: Anticonvulsant Drugs



Examples

- carbamazepine (Epitol, Tegretol)
- clonazepam (Klonopin)
- diazepam (Valium)
- divalproex (Depakote)
- phenytoin (Dilantin)

Anticonvulsant Drugs: MOA

Principle:

Depolarization of nerve: Convulsion

Repolarization of nerve: Returning to normal state

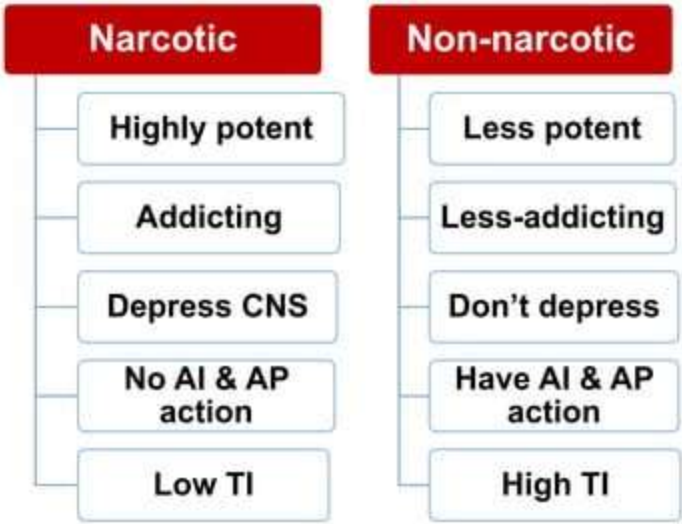
- Blocking of Na^+ channels
- Enhance GABA mediated synaptic inhibition
- Ca^{2+} channel blockade

Analgesics

Narcotic

Non-Narcotic

Narcotic VS Non-narcotic analgesic



Opioid Antagonists…
e.g. Naloxane

Addicting Drugs ….
e.g. Morphine, Heroin

Opioids: Actions & MOA (General)

Actions

- Analgesia
- Respiratory depression
- Constipation
- Urinary Retention
- Cough suppression
- Emesis
- Miosis
- Sedation
- Euphoria/ Dysphoria

MOA

Stimulation of opioid receptors: mu(μ), delta(δ), kappa(κ)

↓

Increase K+ efflux, Reduce Ca+ influx, Decrease cAMP

↓

Inhibition of cell firing

↓

Elimination of pain

CNS Stimulants

Directly acting on CNS:

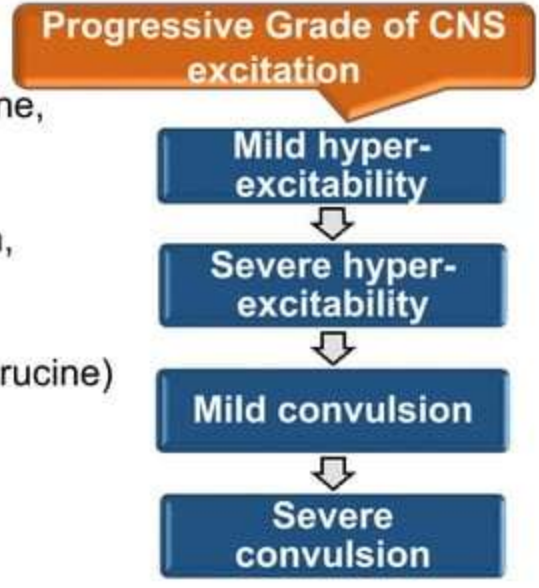
i. **Cortical stimulants** (Amphetamine, Aminophylline)

ii. **Medullary stimulants** (Picrotoxin, Nikethamide)

iii. **Spinal stimulants** (Strychnine, Brucine)

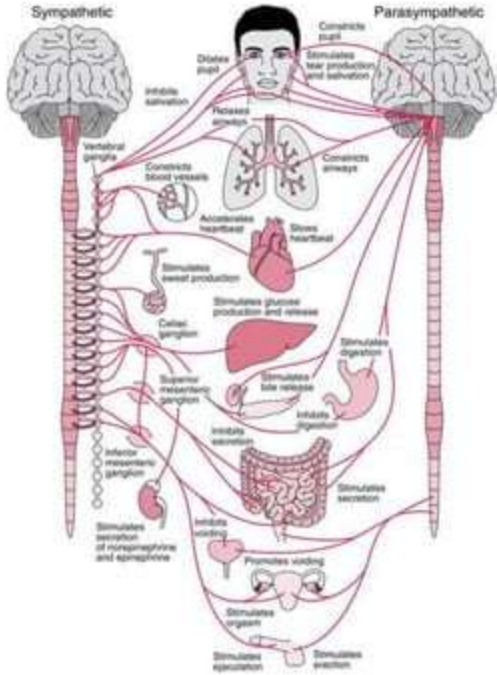
Reflexly acting on CNS:

Nicotine, Ammonia etc.



Miscellaneous

PNS Pharmacology



PNS: Autonomic VS Somatic

SL. NO.	AUTONOMIC	SOMATIC
01	Two neurons…to supply smooth muscles & glands	Single neuron to connect CNS to skeletal muscle
02	Peripheral ganglia present	Peripheral ganglia absent Synapses are entirely within CNS
03	Pr.G. nerves are myelinated Po.G. nerves are non-myelinated	Nerves are myelinated
04	Dessection of nerve: some level of spontaneous activity	Dessection of nerve: Paralysis & atrophy of sk. muscles
05	Ach(ganglia & parasym. Neuroeffector junc.) NE(sym. Neuroeffector junc.)	Ach at neuroeffector junc.

ANS: Classification

Two sets of neurons:

- **Afferent:** Send impulses **to CNS** for interpretation
- **Efferent:** Receive impulses **from the brain** & transmits from the spinal cord **to effector organ cells**

2 branches:

- **Sympathetic NS**
- **Parasympathetic NS**

Preganglionic nerve: connects **CNS to ganglia**
Postsynaptic nerve: connects **ganglia to organs**

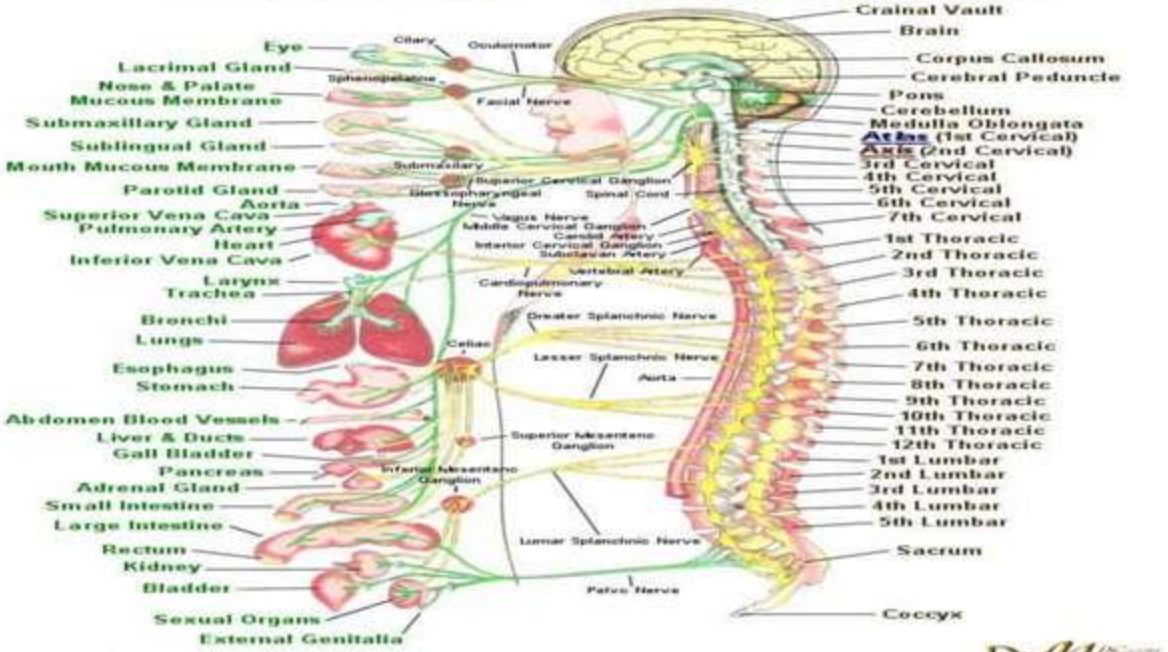
***Ganglia:** Contains nerve endings of pre-G. nerve fibers & cell bodies of post-G. nerve fibers

Sympathetic VS Parasympathetic Nerves

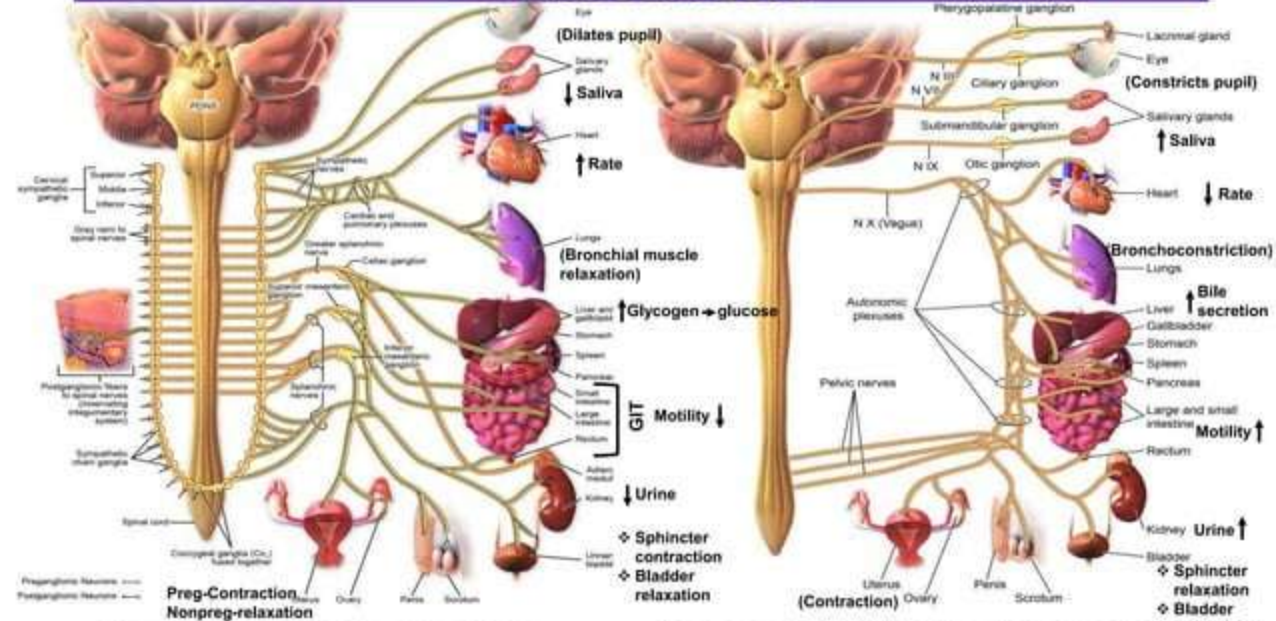
SL. NO.	SYMPATHETIC	PARASYMPATHETIC
01	Arise from thoraco-lumber (T1 to L3) region of spinal cord	Arise from cranio-sacral (III, VII, IX, X, S2 – S4 region of CNS
02	Ganglia are nearer to CNS. Ratio of Pre & PostG. fibers is generally 1: 20 or more. So, PostG. fibers are longer	Ganglia are away from CNS (close to organs). Ratio is generally 1:1. So, postG. fibers are shorter
03	Ach (in ganglia) & NE (at neuroeffector junc.)	Ach in both ganglia & neuroeffector junc.
04	Sym. Activities increases in stress & emergency	Parasym. Activity predominates during rest

Autonomic Nervous System

Sympathetic = Yellow Parasympathetic = Green



ANS ĉ EFFECTS



Sympathetic VS Parasympathetic: EFFECTS

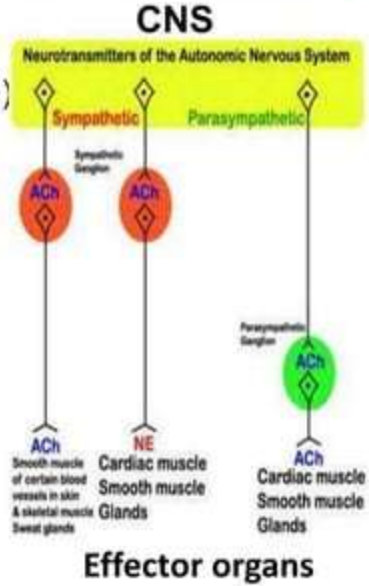
SL. NO.	TISSUES	SYMPATHETIC	PARASYMPATHETIC
01	Eye(Pupil)	Dilation	Constriction
02	Sali. gland	Saliva reduction (Dry mouth)	Increased salivation
03	Heart	Increases heart rate	Decreases heart rate
04	Bronchus	Smooth muscle relaxation	SM contraction
05	Arteries	Constriction	Dilation
06	GIT	Decreased motility, secretion	Increased motility, secretion
07	Liver	Convert glycogen to glucose	Stimulates secretion of bile
08	Bladder	Sphincter contraction & sm relaxation	Sphincter relaxation & sm contraction
09	Kidney	Decreased urine	Increased urine
10	Uterus	Contract(Pg.),Relax(Non-Pg)	Contraction in both condition

ANS: Neuro-Humoral Transmission

Principal neurotransmitters:

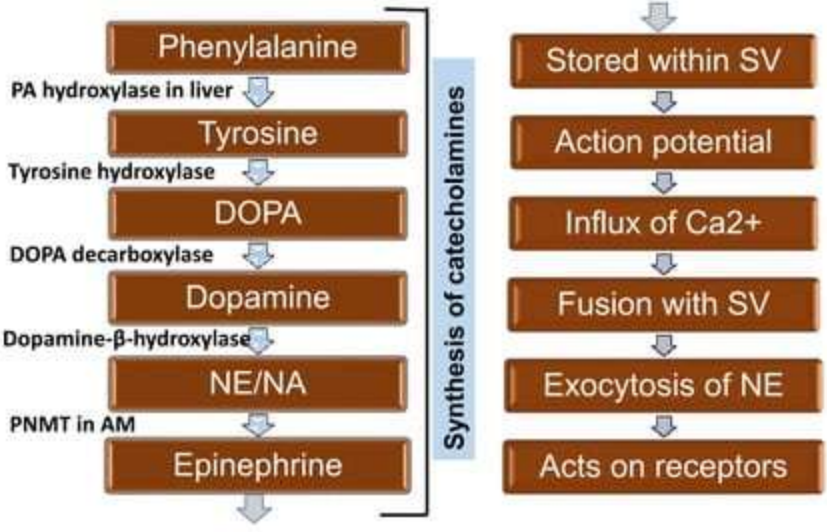
- Sympathetic nerves (adrenergic) : NE or NA (PostG.)
- Parasympathetic nerves (cholinergic): Ach (PostG.)
- PreG. nerve endings of both (Sym. & Parasym.-in ganglia) : ACh

Other neurotransmitters:



ANS: Sympathetic Nervous System (Adrenergic)

Neurotransmitters: NE, E, Dopamine



- **Drugs that mimic action of SNS:** Adrenergic drugs
- **Drugs that inhibit action of sympathomimetics:** Anti-adrenergic/ sympatholytic drugs

SNS (Adrenergic) : Classification

❑ Based on MOA: (3 categories)

i. Direct acting

- ❑ **α agonists**
  - Nonselective
    e.g. NE, Epinephrine
  - Selective (α_1 & α_2 agonists)
    e.g. Clonidine, Phenylephrine
- ❑ **β agonists**
  - Nonselective
    e.g. Isoproterenol
  - Selective (β_1 & β_2 agonists)
    e.g. Dobutamine, Salbutamol

ii. Indirect acting (e.g. Amphetamine)

iii. Mixed acting (e.g. Ephedrine)

SNS (Adrenergic) : Receptors & action

4 types of adrenergic receptors in organ cells:

- **α1 :** Vasoconstriction of blood vessels, Inc. BP, Dec. GI motility, Contracts UB sphincter, Dilates pupil, Contracts uterus
- **α2 :** Inhibits release of NE, Dec. BP, Dec. intestinal secretion
- **β1 :** Inc. heart rate & force of contraction of heart (cardiac stimulant)
- **β2 :** Relaxation of sm in bronchi (Bronchodilator), uterus, peripheral BV, Stimulates insulin secretion

Adrenergic Drugs: Clinical Uses

1) Cardiovascular system

- Cardiac arrest (Adrenaline)
- Heart block (Isoproterenol)
- Cardiogenic shock (Dobutamine, Dopamine)

2) Anaphylactic reaction

- Adrenaline

3) Miscellaneous

- Prolong action of LA by vasoconstriction (Adrenaline)
- Bronchial asthma by Bronchodilation (salbutamol, adrenaline)
- Allergic rhinitis (Adrenaline)
- Dilating pupil (Ephedrine)

Anti-adrenergic Drugs (Sympatholytic Drugs)

Classification

- Adrenergic neuron blockers
  (e.g. Methyldopa, Reserpine)
- Adrenergic receptor blockers
  (α & β antagonists)

α-agonists	β-agonists
α_1 (e.g. Prazocin)	β_1 (e.g. Atenolol)
α_2 (e.g. Idazoxan)	β_2 (e.g. Butoxamine)
Non-selective (e.g. Tolazoline)	Non-selective (e.g. Propranolol)

General Indications

Adverse effects

- Hypotension
- Bradycardia
- Edema

ANS: Parasympathetic Nervous System (Cholinergic)

Neurotransmitter: ACh

Presynaptic neuron & other cells

$CH_3COO^- + ATP + CoA = CH_3COSCoA$

(Acetyl-Co-A)

Choline + Acetyl-Co-A

CAT

Ach (stored in SV)

Action Potential

Opening of Ca^{2+} channel

Influx of Ca^{2+}

Fusion of SV ĉ Axonal membrane

Exocytosis of Ach

AChE in synaptic cleft ⇩ Inhibits ACh

Postsynaptic neuron

Acts on receptor of PostG. Neuron

Action

- **Drugs that mimic action of Parasym. NS:** Cholinergic/ Parasympathomimetic drugs
- **Drugs inhibits action of parasympathomimetics** : Anti-Cholinergic/ Parasympatholytic drugs

Parasym. NS (Cholinergic) : Classification

- **Direct acting** (e.g. Ach, Pilocarpine, Arecoline)
- **Indirect acting**
  - **Irreversible AChE agents** (e.g. Malathion, Carbaryl)
  - **Reversible AChE agents** (e.g. Physostigmine,Neostigmine)

Cholinergic receptors & Responses

Types :

Muscarinic receptors (M_1, M_2, M_3, M_4, M_5) & Nicotinic receptors (N_m, N_n)

Muscarinic responses

- Vasodilation
- Dec. cardiac output
- Inc. GI motility, tone & secretion
- Relax of GI sphincters
- Sweating
- Contracts gall bladder
- Bronchoconstriction
- Causes urination
- Inc. tone & motility of uterus
- Miosis

Nicotinic responses

- ❑ Muscular fasciculations
- ❑ Paralysis (long term action)
- ❑ Release of adrenaline from Adrenal medulla (Inc. BP)

Cholinergic Drugs: Clinical Uses

- Myasthenia gravis* (Physostigmine, Neostigmine)
- Glaucoma: To reduce IOP (Physostigmine 0.5-1%)
- Ruminal impaction (Physostigmine 30-40 mg SC inj. In cattle)
- To control ectoparasites (Carbaryl, Trichlorfon)
- As antidote in atropine poisoning (Physostigmine)
- Urinary retention (Neostigmine)
- In snake bite: specially cobra bite (Neostigmine + atropine to prevent res. Paralysis)

Anticholinergic (Parasympatholytic) Drugs

- **Nonselective muscarinic receptor antagonists** (Atropine, Scopolamine)
- **Selective muscarinic antagonists** (e.g. Pirenzepine-M_1 antagonists)

Clinical uses

- As spasmolytic
- Dec. hypermotility of GIT
- Dec. hypertonicity of uterus, UB, Ureter, Bronchioles
- As pre-anesthetic (Atropine sulfate)
- Peptic ulcer (Pirenzepine)
- To dilate pupil (Homatropine)
- In bronchial asthma (Ipratropium)
- In OPI, carbamate & Myshroom poisoning)
- As anti-parkinsonism drug
- As anti-emetic

Thanks To All