Pharmacology of Central Nervous System

By
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CNS drugs are of major therapeutic & clinical importance.

Drugs can produce diverse physiological & psychological effects as:

- Induction of Anesthesia
- Relief of Pain
- Prevention of Epileptic seizures
- Reduction of Anxiety
  - Treatment of Depression
  - Treatment of Parkinsonism
- Treatment of Alzheimer's disease

Centrally acting drugs include those that are administered without medical intervention like tea, coffee, nicotine, and opiates.
Structure of CNS

- CNS consists mainly of the brain and spinal cord.
- CNS is a highly complex tissue that controls all of the body activities and serves as a processing center that links the body to the outside world.
- Brain formed of 3 main parts:
  I. The forebrain
    • Cerebrum
    • Thalamus
    • Hypothalamus
  II. The midbrain
  III. The hindbrain
    • Cerebellum
    • Pons
    • Medulla oblongata
- **Cerebrum:**
  - The largest part of brain & composed of 2 oval lobes
  - Surrounded by outer cortex known as cerebral cortex
  - **Cerebral cortex** divided into different functional areas:
    1. **Motor areas** (voluntary movements): ↑physical activities.
      - over stimulation cause excitation & convulsions
    2. **Sensory areas** (sensation): wakefulness & sharpness of sensation.
    3. **Association areas** (higher mental activities as consciousness, memory, and behavior).
- **Thalamus:** found in forebrain & contains the pain center
  - Receiving sensory impulses from all parts of body & relays them to sensory areas of the cerebral cortex.
The hypothalamus:
- contain heat regulating center, & appetite center.
- Regulate body temperature, secretions of the anterior pituitary gland.

The mid-brain: connect cerebrum to cerebellum, Pons

Cerebellum: Responsible for balance of the body & maintaining the appropriate body posture & equilibrium.

The medulla oblongata (M.O.):
- Organ of conduction for passage of impulses between brain and spinal cord.
- Contain vital centers as
  - Vagal, vasomotor, respiratory, cough centers.
  - Vomiting & chemoreceptor trigger zone (CTZ)
II- Spinal cord

- A cylindrical mass of nerve cells extend from the end of M.O. to the lower lumbar vertebrae.
- Impulses flow from and to the brain through descending and ascending tracts of the spinal cord.
- Act as a reflex station for receiving impulses from and to all parts of the body.
- Contain sex centers (Erection and ejaculation), sweat and micturation centers.
Pharmacology of Synaptic transmission

Propagation of action potentials → Calcium entry → Transmitter release → Receptor events
Transmission in C.N.S.

- A nerve impulse (electric current) passes along axon to presynaptic membrane.
- Release neurotransmitter into synaptic cleft.
- NT interacts with receptors on effector cells to induce response.
- NT released into synaptic cleft in response to action potentials - release is voltage dependent & require calcium influx (Neuroregulators).
A nerve terminal

- Synthesis
- Storage
- Neurotransmitter Vesicles
- Mobilization
- Release (Ca$^+$ dependent!)
- Postsynaptic membrane
- Effector Cell

Presynaptic membrane

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Life of a transmitter

1. Synthesis
2. Release
3. Effects
4. Removal
Amino acids & Amine Transmitter in CNS

- **Glutamate** - major excitatory transmitter
- **Aspartate**
- **GABA** - major inhibitory transmitter
- **Glycine**
- **Acetylcholine** - mixed effects
- **Monamines:**
  - **Noradrenaline** - mixed effects
  - **Adrenaline** - mixed effects
  - **Dopamine** - mixed effects
  - **5-HT** - mixed effects
Glutamate & Aspartate

- Major **excitatory amino acids** transmitters
- Excitation due to depolarization of postsynaptic membrane of neuron
- by acting on glutamate & aspartate subtype receptors
- Location: Interneuron at all levels (spinal & brain)
- Blocked by Ketamine.
Gamma amino butyric acid (GABA)

- Major inhibitory transmitter at all levels of brain
- Inhibition results from hyperpolarization produced by increase chloride conductance
- GABA acts on GABA receptors → opening of linked chloride channel → hyperpolarization.
- GABA is a ligand-gated Cl⁻ channel.
- Fast inhibition through GABA-A R.
- Slow inhibition through GABA-B R.
  - Barbiturates, Sod. Valporate & ivermectin → increase binding
  - of GABA to its receptors (GABA Agonist)
**Picrotoxin**: antagonize GABA by closing chloride channel

⇒ inhibit presynaptic & postsynaptic inhibition of GABA causing stimulant effect
Acetylcholine (Ach)

- Important transmitter in CNS
- Ach widely distributed in major parts of CNS
- Both types of Cholinergic receptors (nicotinic & muscarinic) occur in CNS
- Acetylcholine in the brain plays a role in
  - 1- Arousal
  - 2- Learning
  - 3- Short term memory
- Loss of cholinergic neurons in the memory site is associated with "Alzheimer’s disease"
Monoamines
Noradrenaline, dopamine & 5-HT

- Found in all levels of brain: midbrain, stem & peripheral neurons
- Noradrenaline play important role in
  1- Mood: Deficiency of NA in brain cause depression.
  2- Arousal: Increase release NA in brain ⇒ wakefulness
- Dopamine is the major neurotransmitter act on dopamine R.
- Dopamine play role in
  1- control motor function: Deficiency cause “Parkinson’s disease”.
  2- Behavioural effects: control of behavior and emotion.
5-Hydroxytryptamine (5-HT)

- 5-HT is an important CNS transmitter
- 5-HT plays a role in
  1. Mood: useful in depressive states.
  2. Sensory transmission: inhibits transmission of pain impulses & enhances morphine analgesia.
  3. Temperature control
- 4. Vomiting: 5-HT blocker used as anti-emetic.

**Pain, migraine, anxiety, depression, hallucinations, fear & attention**
Drugs acting on CNS

CNS Stimulants
- Cerebral stimulants
- Medullary stimulants
- Spinal cord Stimulants

CNS Depressants
- Nerve Sedatives
- Tranquilizers
- Hypnotics
- Anticonvulsants
- Anaesthetics
- Analgesics
**Cerebral stimulants**

*(Cerebral -cortex stimulants)*

- Stim. motor & sensory area so ↑ physical & mental activity
- Wakefulness, refreshment, ↓ fatigue.
- Awake animals from anesthesia in Vet. Med.
- **Xanthines** (Caffeine, theophylline & Theobromine),
- Amphetamine & Retaline.
  - **Caffeine** (coffee seeds), **theophylline** (tea leaves)
  - **Theobromine** (coca seeds) & methylated Xanthine.
- **MOA**: Caffeine Inhibit phosphodiesterase enz. so ↑ c-AMP in cerebral cortex neurons.
Pharmacological Effects

1- Smooth muscle relaxant (spasmolytic)  *Aminophylline*.

2- Cardiac stimulant: increase force of contraction (+ve inotropic) & increase Heart rate (+ve chronotropic) → increase BL. Pressure
   - coronary V.D & vagal stim. decrease BL. Pr.
   - Both effects lead to slight rise in BL. Pressure
   - Caffeine is contraindicated in hypertensive patients.

3- Secondary diuretic:
   - Increase renal Bl. Flow due to cardiac stimulant effect.
   - Renal vasodilatation → increase glomerular filtration.
   - Inhibit release ADH → decrease water reabsorption.
   - Decrease Na tubular reabsorption.
4- GIT: caffeine increase gastric secretions ⇒ improve digestion.

**Therapeutic uses:**
- Antagonize cortex depression & awake animal from anesthesia.
- Caffeine combined with Aspirin or Paracetamol for treatment of Headache
- For Oedema
- Aminophylline used for bronchial asthma
- For billiary, renal & intestinal colic (spasmolytic).
<table>
<thead>
<tr>
<th>Differences</th>
<th>Caffeine</th>
<th>Theophylline</th>
<th>Theobromine</th>
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<tbody>
<tr>
<td>Plant origin</td>
<td>Coffee</td>
<td>Tea</td>
<td>Coca</td>
</tr>
<tr>
<td>Cerebral stim.</td>
<td>powerful</td>
<td>Moderate</td>
<td>Weak</td>
</tr>
<tr>
<td>Cardiac stim.</td>
<td>Weak</td>
<td>Powerful</td>
<td>Moderate</td>
</tr>
<tr>
<td>Diuretic</td>
<td>Weak</td>
<td>Powerful</td>
<td>Moderate</td>
</tr>
<tr>
<td>Sm. ms. Relax.</td>
<td>Weak</td>
<td>Powerful</td>
<td>Moderate</td>
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**Amphetamine (Benzedrine):**

- Powerful CNS stimulant; ↑ mental & muscular activities.
- Non catecholamine, stimulate α & β receptors by inhibit MAO enz.
- Increase basal metabolic rate → for treatment of obesity.

**Therapeutic uses:** Illegally as a motor activator for race horse (doping).
- For tt. of CNS depression in barbiturate & narcotic poisoning.
Medullary stimulants

Direct medullary stimulants
- Picrotoxine
- Nikethamide
- Cardiazol
- Bemegride
- Doxapram

Reflex medullary stimulants
- Camphor
- Ammonia Sol.
Medullary stimulants (analectics)

Drugs stimulate centers of M.O. especially depressed resp. C.

Awake anaesthetized animal by stim.brain & M.O. centers.

Picrotoxine:

✓ Powerful stimulant on resp. & vasomotor centers.
✓ Raised blood pressure & ↑ respiration.
✓ MOA: 1- Antagonize GABA by closing Cl⁻ channel ⇒ inhibit pre- and postsynaptic inhibition caused by GABA.
✓ 2- Stim. chemo receptors at aortic sius in heart → stim. heart
✓ For ttt. barbiturate poisoning (given i.v. or i.m)

Nikethamide (coramine): Given orally - has no effect on heart
Less effective & Less toxic than picrotoxine.
Cardiazol (Leptazol)

- Stim. resp. & vasomotor centers no effect on heart.
- For ttt anesthesia & narcotic poisoning (i.v.). L.D. → convulsions

Bemegride

- Powerful respiratory stimulant in barbiturate poisoning.
- MOA: Competitive antagonism with barbiturate due to chemical similarity (given i.v.)

Doxapram

- The most powerful analeptic - has wide safety margin.
- Act both centrally & peripherally.

Camphor & Ammonia solution (Reflex analeptic)

- Camphor s/c → irritate cut. S. Ns. → reflexly stim. M.O. respt. C.
Spinal cord Stimulants

Strychnine:

- Alkaloid from *strychnus nux vomica* seeds.
- **MOA:** 1- inhibit inhibitory transmitter glycine at post-synaptic N.E. so increase reflex excitability to external stimuli.

2- On brain St. Sensory area of cerebral cortex ⇒ sharp sensation

Large dose ⇒ convulsions of sk.ms & diaphragm.

Aphrodisiac (for ttt sexual impotency in dogs).

General tonic & stomachic (for anorexia, weak depilating A.)

Neuromuscular purgative (stim. aurbach’s plexus of intestine)

Ruminal tonic (For ruminal atony)

used as Motor activator for race horses (doping) to ↑ capacity for running
Strychnine Toxicity

- Toxicity due to large toxic dose or Cumulative effect

- **Toxic symptoms**: convulsions in all sk.ms & diaphragm.

- Poisoned dog show ch. posture [back become arched, limbs become rigid & extended, head raised upward & backward & tail raised upward]

- Convulsions interrupted by period of rest or relaxation (Tonic C.)

- Death due to asphyxia as a result of prolonged contraction diaphragm m

- **Treatment**: Dark Place – Artificial Respiration- Volatile Anesthetic

- **Specific Antidote**: chloral hydrate (For horse). Barbiturates or Bromides (dogs). Mephenesin (For Man, central sk. ms.relaxant).
CNS Depressants

- Classified according to degree & type of depression

Nerve sedatives

Tranquilizers

Sedative Hypnotics

Anticonvulsant

Anesthetics

Analgesics
Tranquilizer and Sedatives

Nerve Sedatives: depress CNS, produce sedation, drowsiness, unaware to surroundings, decrease loco motor activity and reduce fear but animal remain conscious.

The large dose induces loss of consciousness & hypnosis so called sedative hypnotics.

Tranquilizer Sedatives:

Reduce anxiety & induce calming without loss of consciousness even with large dose.

Drug cannot induce only one pharmacologic effect but according to dose...
Chloral hydrate & bromides

- Chloral hydrate → **Nerve sedative** at small dose
- **Hypnotic & General anesthetic** at L.D. for **horse** (by i.v.).
- **MOA:** In liver reduced into **trichloroethanol** ⇒ depress CNS
- **Disadvant:** Narrow safety margin – irritant ⇒ tissue necrosis.
- Slow induction, prolonged recovery periods
- Depress Res. C.& heart ⇒ Res.failure & hypotension (L.D)
- **Uses:** for ttt flatulent colic in ruminants (orally with turpentine oil)
- For horse used as a sedative or general anesthetic.
- For dogs given with bromide for strychnine poisoning, epilepsy
Bromides (potassium salts & sodium salts)

- Pot. bromide salts act as a nerve sedative & anticonvulsant
- **MOA:** Bromide stabilize neuronal cell mm by interfering with chloride transport across cell mm (replacement with \( \text{cl}^- \) in extracellular fluid of N.C, so decrease \( \text{cl}^- \) conc. → sedation
- depress only motor area of cerebral cortex
- Bromide used for ttt epilepsy & strychnine poisoning.
- For dogs used as anaphrodisiac to suppress sexual excitability (depress the sex centers in spinal cord).
Tranquilizers (Neuroleptics)

- Tranquilizer relieve anxiety and mental tension in man.
- In animals, quieting & calming effect and reduce fear
- **Clinical Uses:**
  - Used to Calm vicious animals to facilitate clinical examination.
  - Before transportation of animals to reduce fear & prevent vomiting
  - As preanaesthetic medication to volatile anaesthetics.

**Examples:** *Phenothiazines*

- Acepromazine - Chlorpromazine - Promazine

**Butyrophenones:** [Azaperone] – Diazepam - Midazolam
Hypnotics produce normal sleep & deep sleep (narcosis) or general anaesthesia at LD

- Chloral hydrate
  - $\alpha_2$-adrenoreceptor agonist
    - xylazine
    - Detomidine

- Barbiturates

- Benzodiazepine
  - Diazepam
  - Zolazepam

Sedative hypnotics
**Difference between hypnotics & tranquilizers**

<table>
<thead>
<tr>
<th>Effect of high dose</th>
<th>Sedative hypnotics</th>
<th>Tranquilizer</th>
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<tbody>
<tr>
<td>Loss consciousness</td>
<td>- Anesthesia</td>
<td>- Conscious.</td>
</tr>
<tr>
<td>- Resp. depression</td>
<td></td>
<td>- only immobility</td>
</tr>
<tr>
<td>NO resp.dep</td>
<td></td>
<td>NO resp.dep</td>
</tr>
</tbody>
</table>

| Reflex sensory s    | - Depressed        | - Normal     |

| Effect on emesis    | - No effect        | - inhibition of CTZ |

| Anticonvulsant      | - General sk. ms. relax | Limited & specific |

| preanesthetic       | - Duration not affected | - Prolong duration |
**Xylazine (Rompun)**

- A sedative hypnotic, Analgesic & skeletal muscle relaxant effects
- Xylazine is $\alpha_2$- adrenoceptor agonist
- **MOA:** by stimulation of $\alpha_2$- receptors in sympathetic nerves.
- Ruminants most respond to xylazine
- Low dose $\rightarrow$ sedation, high doses $\rightarrow$ recumbence
- **Clinical Uses:** Given by i.m. or i.v.
- To Calm vicious animals before clinical exam.
- Preanesthetic medication.
- For ttt. Spasmodic colic
- Treatment of skeletal muscle convulsions as an anticonvulsant.
Barbiturates

- Derivative of barbituric acid
- Have a gradual degree of CNS depression from
- Sedative Hypnotic to General anesthetic
- Good skeletal muscle relaxant, but lack analgesic effect.
- Highly irritant sol given i.v.

Classif.:

- Long acting barbiturates: Phenobarbital sod. 6-8hs.
- Medium: Hexobarbital 4-6hs.
- Short: Pentobarbital (Nembutal)® 2-4hrs.
  - Secobarbital (Seconal)®
- Ultra short: Thiopental (Nesdonal)® ¼ -2hrs.
- **MOA:** Interfere with ATPases in cerebral cortex → prevent its utilization → depression.

- **Kinetics:** IV inj. → distribute in Bl. Brain & localized in adipose Ts.

- Duration of action depends on rate of metabolism & excretion.

- Enhance metabolism of other drugs (**Microsomal inducer**).

- **Uses:** As preanaesthetic for induction of general anaesthesia.

- For strychnine poisoning.

- For epilepsy & canine distemper.

- **Toxicity:** Respiratory depression, weak pulse, hypotension, hypothermia, coma and death.

- **Treatment:** By analeptics (nikethamide i.v. every 15-30min.)
**Goals for preanesthetic medication**

- Reduce anesthetics dose.
- Reduce undesirable side effects (Vagal & secretions)
- Minimize pain & provide analgesia
- A smooth anesthetic induction & recovery
- Complete sk.ms relaxation.

1. Sedative hypnotics, tranquilizers & analgesic

2. **Atropine**: reduce salivary & bronchial secretions. \(\uparrow\) heart rate & stimulate respiration (\(\uparrow\)R.C.)

3. Skeletal muscle relaxants:
Major drugs for preanaesthetic medication

1- Tranquilizer & sedative:
   a. Acepromazine.
   b. Diazepam.
   c. Midazolam.
   d. Droperidol.

2- Hypnotic-sedative:
   a. Pentobarbital.
   b. Chloral hydrate.

3 - $\alpha_2$-adrenergic agonist:
   a. Xylazine.
   b. Detomidine

4- Parasympatholytic
   Atropine.

5- Opioid analgesic:
   a. Morphine.
   b. Meperidine
Anticonvulsents

Specific
- Diazepam
- Primidone
- Sod. Valporate
- Phenytoin
- Clonazepam
- Mephenesin

Non specific
- Phenobarbital
- Bromide salts.
- Xylazine
- Gallamine
- Tubocurarine
Convulsions (Seizures): result by stimulation of spinal cord or motor area of cerebral cortex.

Epilepsy: acute prolonged recurrent seizures.

Anticonvulsants (Antiepileptic):

Drugs used to Stop Ongoing Seizure Activity & to decrease frequency, severity of future seizures.

In epileptic crises, treatment is essential to prevent death.

Diazepam the drug of choice for controlling epileptics & stopping seizures in both small & large animals [rapid onset of action that prevents spread of seizure]

Benzodiazepines [diazepam, Clonazepam, clorazepate]
**Phenobarbital:** orally

- Drug of choice for long-term seizures control for dogs & cats.
- ↓ spontaneous depolarize. in brain, prevent spread.

**Phenytoin:**

- Poorly absorbed from GIT, & rapidly eliminated by liver.
- Must given 3 times daily to maintain Bl. therapeutic level.

**Benzodiazepine (Diazepam & clonazepam).**

- Used as anxiolytics in behavioral medicine.
- Diazepam used for ttt. seizure related aggression in dogs.
- **Diazepam:** drug of choice for emergency treatment (IV).
- By enhancing inhibitory effect GABA ⇒ quiet activity CNS.
Psychotropic Agents

- Anxiolytics, Antipsychotics, Antidepressants, & mood stabilizers used to treat human behavioral disorders
- used more commonly in Vet Med for behavioral modification therapy
- Anxiolytics: [benzodiazepines & azapirone (buspirone)]
- used to treat generalized anxiety and panic disorder in dogs and cats, as well as urine spraying in cats.
- Benzodiazepines (diazepam, alprazolam, oxazepam, clorazepate) act by binding to \(\gamma\)-amino butyric acid (GABA) receptors
- Buspirone block serotonin and acts as a dopamine agonist