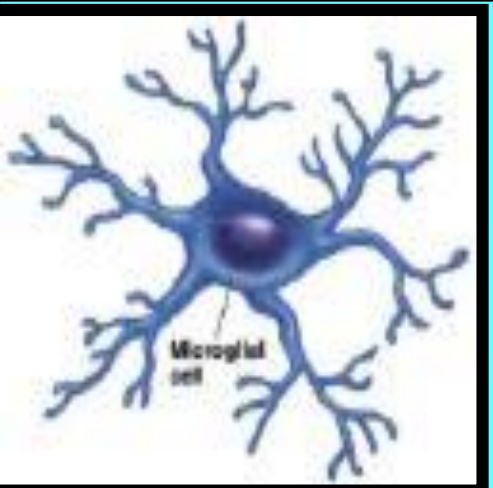
بسم الله الرحمن الرحيم

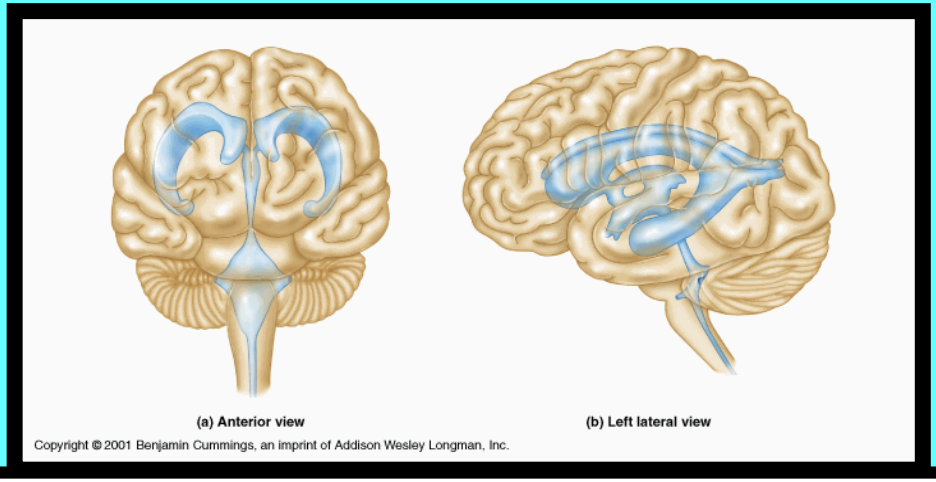
قالوا سبحانك لاعلم لنا إلا ماعلمتنآ إنك أنت العليم الحكيم ۝

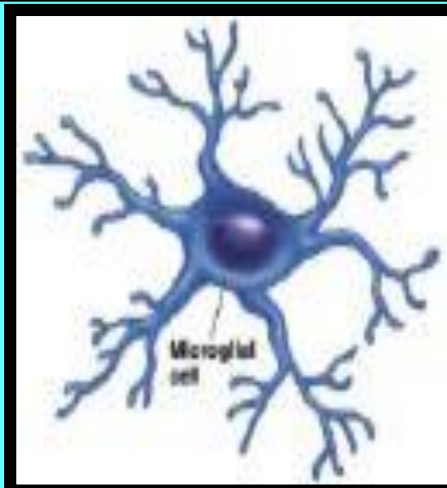
صدق الله العظيم

سورة البقرة الآية (32)

Drugs Acting on CNS







BY

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Anatomy of CNS

CNS mainly consists of

I-Brain

1-Cerebrum
(Motor area, Sensory area)
2-Cerebellum
3-Thalamus
4-Hypo-thalamus

II-Medulla oblongata

- Vagal Center
- Vasomotor Center
- Vomiting Center
- Respiratory Center
- Cough Center

III-Spinal cord

extend in vertebral column

- Sex Center
- Sweat Cen.
- Micturation center

Anatomy of CNS

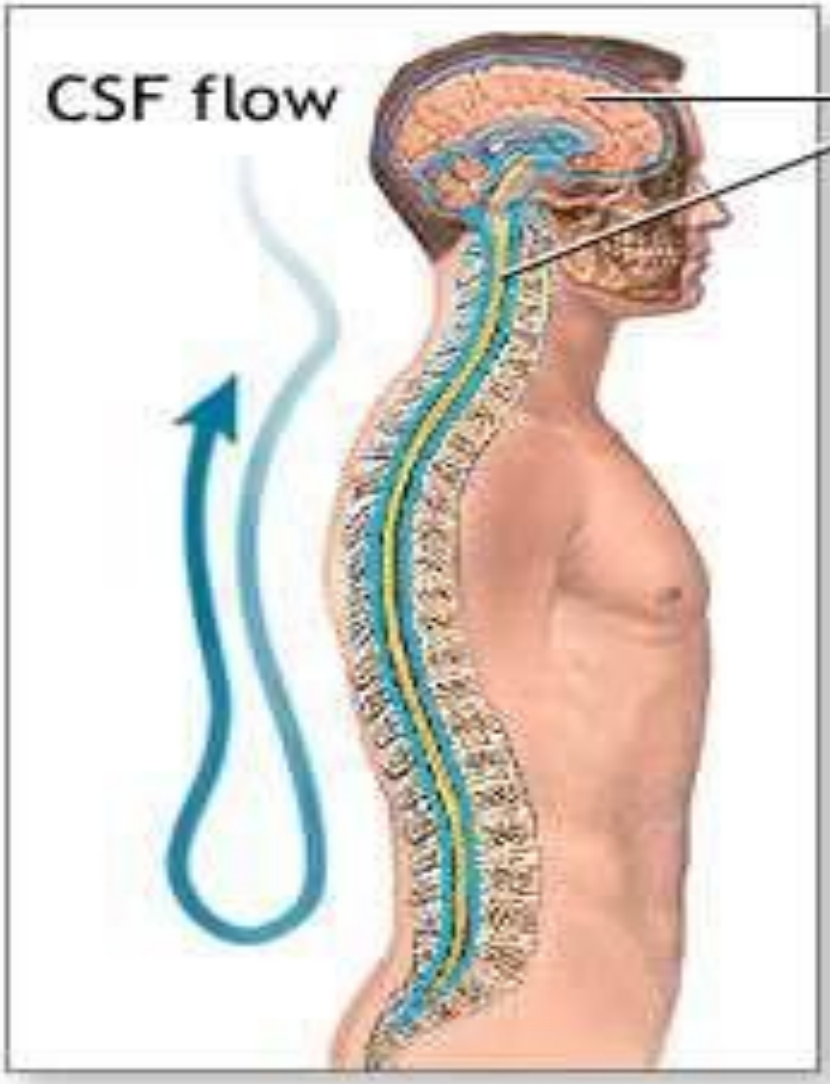
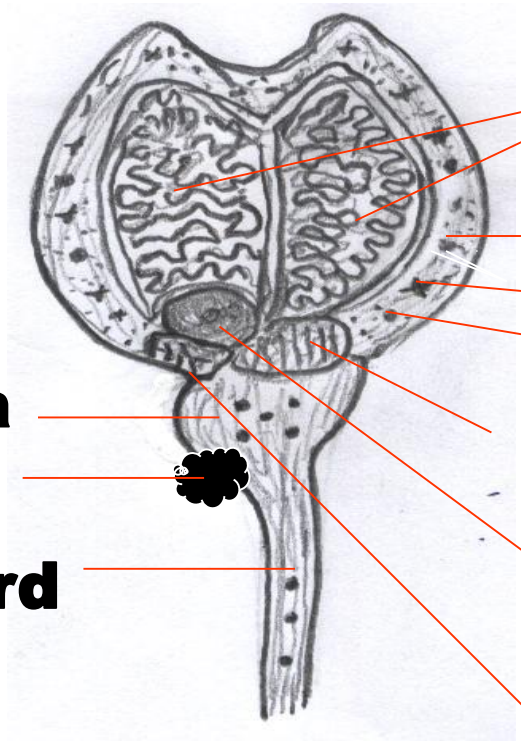


Diagram of CNS Anatomy

Brain



Cerebral hemispheres

Cerebral cortex

Sensory area

Motor area

Cerebellum

Medulla oblongata

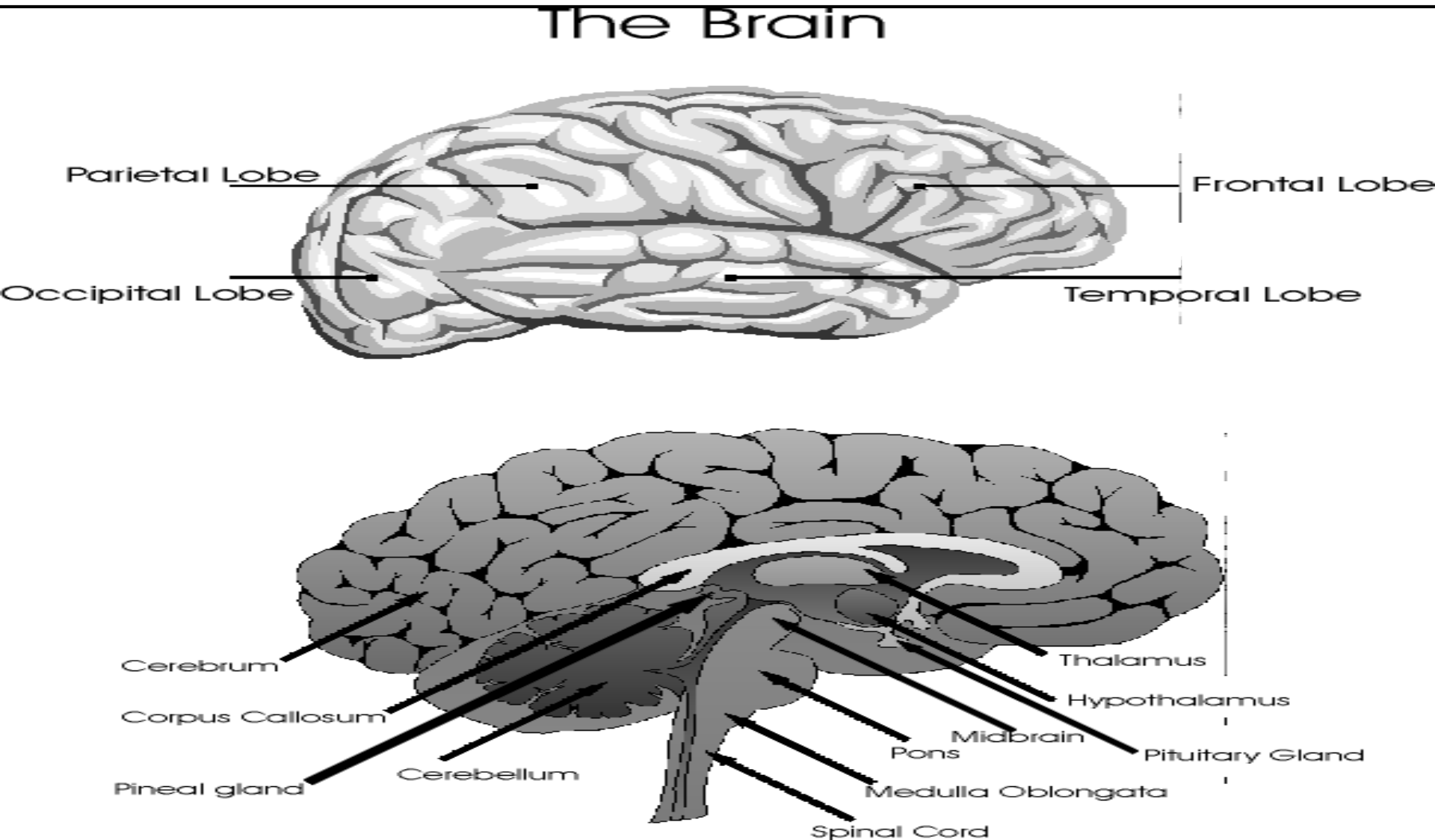
CTZ

Spinal cord

Thalamus

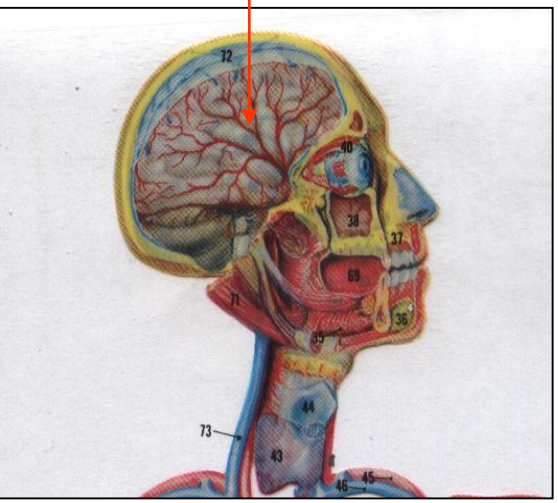
Hypothalamus

The brain and CNS



Gross Anatomy of CNS

Blood vessels of the brain



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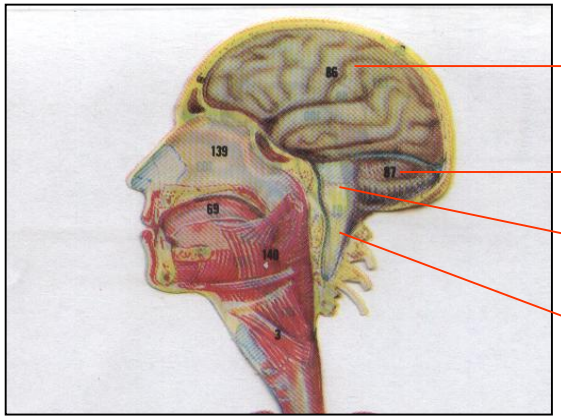

Cerebral hemispheres

Cerebellum

Medulla oblongata

Spinal cord

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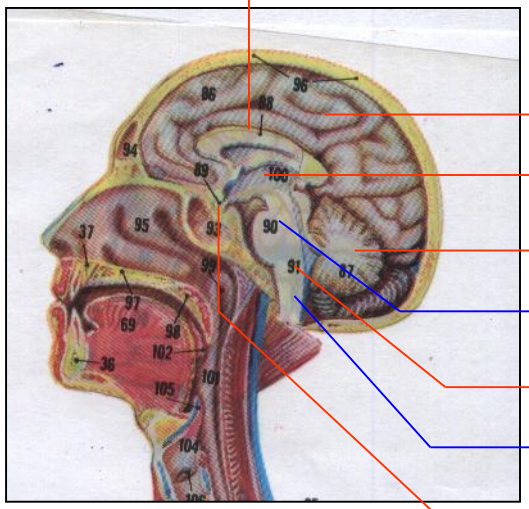


Pons

Cerebral hemisphere

3 rd ventricle

Cerebellum

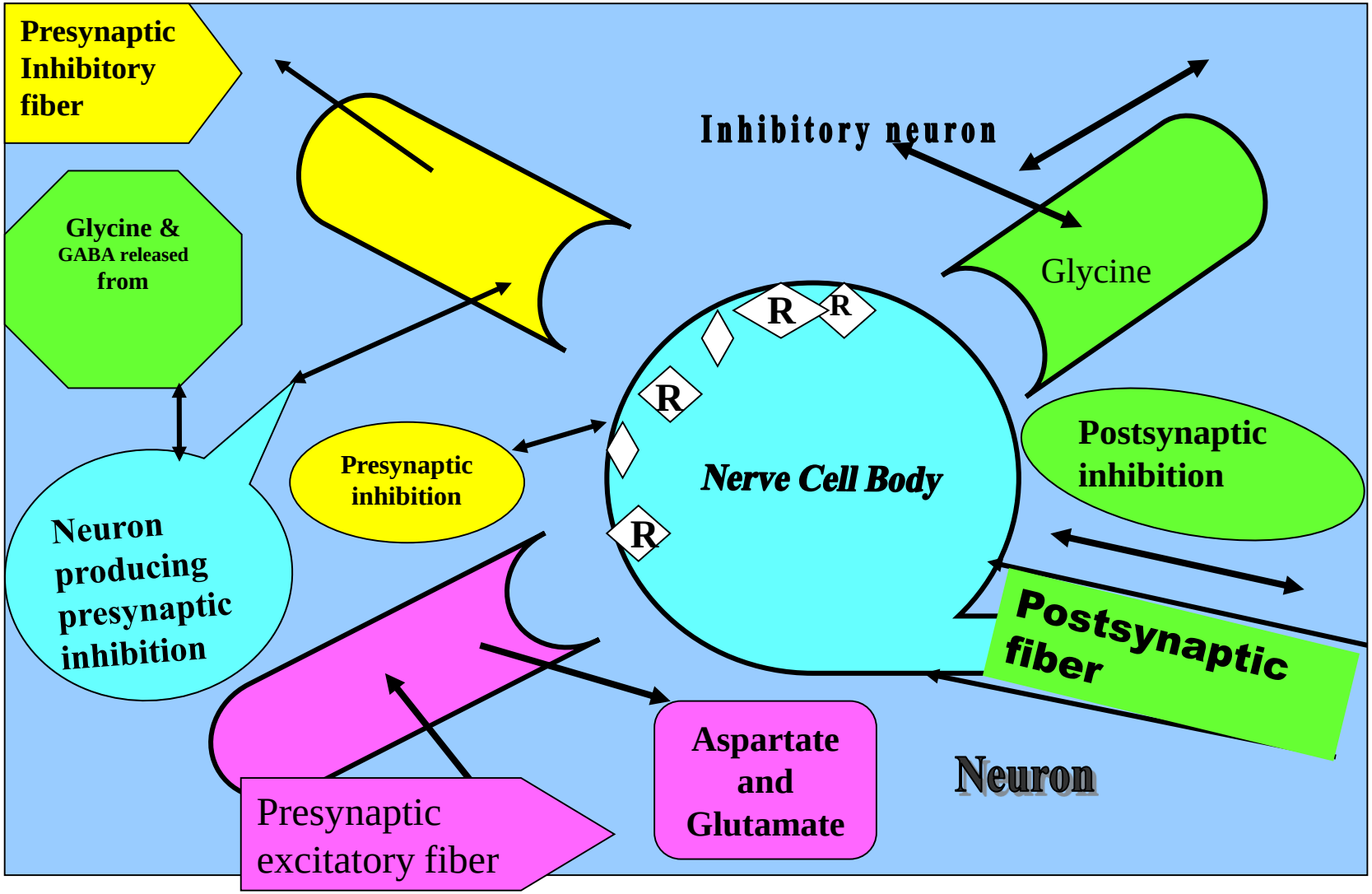
Medulla oblongata

Varol Bridge

Spinal cord

Pituitary gland

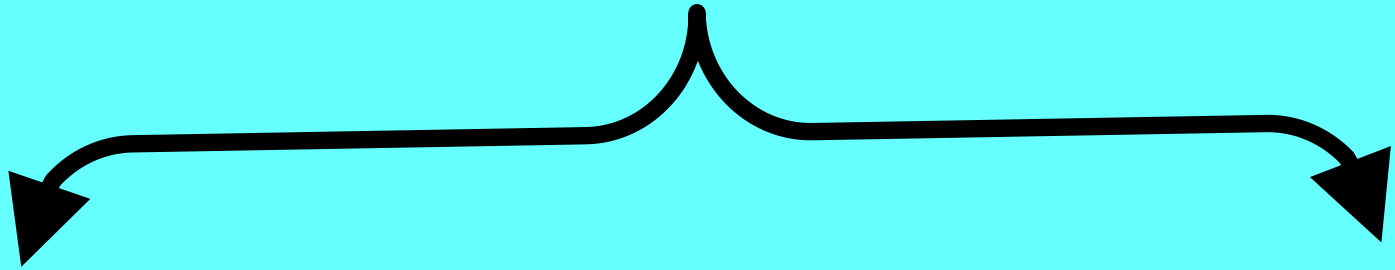
Transmission in CNS



Amino Acids and Neurotransmitters in CNS

Type	Transmitter	Action
1-Excitatory amino acids	Glutamate and aspartate	Stimulation due to depolarization by acting on glutamate and aspartate subtype-receptors
2-Inhibitory amino acids	Glycine and GABA	Inhibition due to hyperpolarization produced by increase chloride conductance
3- Choline ester	Acetylcholine (Ach)	Stimulation and inhibition on central nicotinic receptors Stimulation of peripheral muscarinic receptors
4-Adrenergic drugs	Adrenaline Noradrenaline Dopamine 5- HT	Stimulation on α and β receptors. Dopamine act on dopamine receptors (Central and peripheral)

Classification of CNS Drugs



I- CNS stimulants

1- Cerebral stimulants

2- Medullary stimulants

3- Spinal cord stimulants

II- CNS depressants

1- Nerve sedatives

2- Anticonvulsants

3- Tranquilizers

4- Hypnotics

5- Anaesthetics

6- Analgesics

1- Cerebral Stimulants

■ **Definition :** Are drugs which increase the functional activity of neurons in the cerebral cortex and stimulate motor and sensory areas so cause wakefulness and refreshment in man. They are used in case of mental and muscular fatigue. In Vet. Med., they are used to awake animals from anaesthesia.

■ **Classification :**

1-Classical stimulants: •Xanthine derivatives •Amphetamine •Retalin

2-Antidepressants: •Imipramine •Desipramine

3-Psychotomimetics: •Mescaline •LSD

- **Xanthine derivatives:**
- **Caffeine**
- **Theophylline**
- **Theobromine**

1- Xanthine Derivatives

They include: • Caffeine • Theophylline • Theobromine

- **All are alkaloids from plants**
- **All are methylated xanthine**
- **All have the same actions and mechanism of action, but they differ in their potency and therapeutic uses.**
- **Actions of caffeine:**

1- Cerebral stimulant **2- Smooth muscle relaxant**

3- Cardiac stimulant **4- Secondary diuretic**

5- On GIT : Caffeine increases gastric secretions so it is contraindicated in patients with gastric ulcer.

1- Mode of action of caffeine as cerebral stimulant:

It inhibits phosphodiesterase enzyme in neurons of the cerebral cortex → increases the amount of cyclic Adenosine monophosphate (c-AMP) → increases mental and muscular activity and reduces feeling by fatigue. It reduces the pain of headache as it causes constriction of cerebral blood vessels. So it is used with aspirin for headache, muscular fatigue, pain and fever in man.

2- As smooth muscle relaxant: Caffeine inhibits directly the smooth muscle of the bronchi (spasmolytic effect), but aminophylline (a derivative of theophylline) is more powerful bronchial dilator and used for treatment of bronchial asthma.

3- As cardiac stimulant: In small doses, caffeine stimulates the cardiac muscle directly by increasing Ca++ ions influx to the myocardium and increase force of contractility.
Moreover, it causes coronary vasodilatation and vagal center stimulation, so lower blood pressure. Both effects produce a slight rise in blood pressure, so caffeine is contraindicated in hypertensive patients.

4- As secondary diuretic Caffeine:

- Increases renal blood flow due to its cardiac stimulant effect.
- Causes renal vasodilatation so increase the GF.
- Increases the number of active functioning glomeruli so increase the amount of GF.
- Inhibits the release of ADH, so decreases water reabsorption from the renal tubules to the blood.

Therapeutic uses of caffeine:

1- For **respiratory depression** and to awake animals from anesthesia

2- For **headache and fever** given with aspirin

3- For **edema** due to congestive heart failure

Differences	Caffeine	Theophylline	Theobromine
Plant origin	Coffee seeds	Tea leaves	Coca seeds
Chemistry	1,3,5 Trimethyl Xanthine	3,5 Dimethyl Xanthine	1,3 Dimethyl Xanthine
Effects: Cerebral Stim.	+ + +	+ +	+
Cardiac Stim.	+	+ + +	+ +
2nd Diuretic	+	+ + +	+ +
Sm. M. relax.	+	+ + +	+ +

■ **2- Amphetamine (Benzidrine):** It has a stimulant effect on **both CNS** & **sympathetic nerves**. It increases mental and muscular activity, so used in **barbiturate** and narcotic poisoning. It is **illegally** used as an activator for race horses **(doping)**. It causes **rise in BP** due to stimulation of sympathetic nerves via inhibition of **(MAO)** monoaminoxidase enzyme

■ **3- Retalin:** It is a **synthetic** chemical comp. which act as a cerebral stimulant like caffeine It has **no effect on blood pressure**. It is used in case of **narcotic** poisoning.

2-Medullary Stimulants (Analeptics)

- **Definition:** Are drugs which stimulate the **vital centers** in M.O. especially the **depressed respiratory center**.

classification

Direct

- Picrotoxine
- Nikethamide (Coramine)
- Cardiazol (Leptazol, Metrazol)
- Bemegride
- Doxapram

Reflex

- Camphor (s/c)
- Ammonia sol.(Inhalation)

1-Picrotoxine:

- Alkaloid from *Anamirta cocculus* seeds
- Powerful respiratory stimulant by: 1- inhibiting **GABA** transmitter at **presynaptic** nerve endings 2- stimulating **chemoreceptor** at the aortic sinus in the heart so stimulate the heart and circulation.
- Used in **barbiturate** poisoning and given i.v. or i.m.
- Toxic for non-anaesthetized animals (convulsion and hypertension).
- It is used as a **fish poison**.

2-Nikthamide (coramine): It is a **nicotinic acid** derivative similar to picrotoxine but it is:

a- **Less** effective

b- **Less** toxic

c- Has **no effect** on the heart

d- Given **orally**

3- Cardiazol (leptazol) : Stimulate respiratory and vasomotor centers, but has **no effect on the heart**. It is used in **deep anaesthesia** or narcotic poisoning and given i.v. Its large doses cause muscular **convulsions**.

4-Bemegride: powerful respiratory stimulant in barbiturate poisoning. It act by **competitive antagonism with barbiturates** due to their chemical similarity. It is given i.v. and its large doses cause muscular **tremors and convulsions.**

5- Doxapram: The most powerful analeptic with a wide safety margin. It acts both centrally by direct stimulation of respiratory center and peripherally by stimulation of CRs in the aortic and carotid body in the heart. Its respiratory stimulant effect is short and may be followed by secondary respiratory failure.

6- Camphor: It is a reflex analeptic when injected S/C cause irritation of the cutaneous sensory nerves so it reflexly stimulate medullary centers. It is used in coma or respiratory depression . Externally, it used as a counter irritant for rheumatic pain.

7- Ammonia solution: Reflex analeptic after inhalation it causes irritation of the sensory nerve endings of the nose and reflexly stimulates the respiratory center. When given orally after dilution, it irritates the sensory nerves of stomach which reflexly stimulate the respiratory center. It is used in cases of coma and respiratory depression.

3- Spinal Cord Stimulants

- **Definition:** Are drugs which stimulate spinal cord and centers in it so increase the muscular activity and reflex excitability to external stimuli.
- **Examples:** 1- Strychnine (+++) 2- Brucine (+)

Strychnine

- **Origin:** Alkaloid from strychnus nux vomica seeds.
- **Actions:** 1- Spinal cord stimulant: by inhibition of the inhibitory transmitter glycine that released by Renshow cells at post-synaptic nerve endings, so increase the reflex excitability to external stimuli.

Its large doses cause convulsion of skeletal muscles and diaphragm.

2- Aphrodisiac: by stimulating sex centers in the spinal cord (Sex Impotency)

3- General tonic and stomachic: Orally it stimulates taste buds of the tongue and gustatory buds of stomach so improve appetite (Anorexia)

4- Neuromuscular purgative: by stimulation of Aurbach's plexus of the intestinal mucosa, so increase the intestinal motility.

5- Ruminal tonic: by increasing the ruminal motility (Ruminal atony)

Therapeutic uses of strychnine:

1- For weak and debilitating animals as a general tonic

2- For ruminal atony as a ruminal tonic

3- For sexual impotency in males as aphrodisiac

4- It is illegally used as a motor activator for race horses to increase their physical activity for running (doping)

5- It is used as a poison for stray dogs.

Toxic symptoms of strychnine in dogs:

1- Convulsions in all skeletal muscles and diaphragm

2- Characteristic posture (opisistonous form)of the animal

3- Tonic convulsions i.e. interrupted by periods of rest

4- The period of convulsion increased by increasing the dose

5- Death occurs due to asphyxia by contraction of diaphragm M

Treatment of strychnine poisoning:

1- Keep the animal in a dark place 2- Artificial respiration

3- Inhalation of volatile anesthetic as chloroform

4- Administration of antidotes: in dogs give barbiturates or bromides, in horses give chloral hydrate and in man give mephenesin (Sk. M. Relaxant)

(II) CNS Depressants

(1) Nerve sedatives

■ **Definition:** Are drugs which depress CNS and cause drowsiness and unawareness to the surroundings. They decrease the locomotor activity and reduce fear, but the animal remains conscious.

A- Sedative hypnotics → Produce loss of consciousness

B- Tranquilizer hypnotics → Doesn't produce loss of consciousness

The commonly used nerve sedatives are chloral hydrate and bromides.

1- Chloral hydrate [$Ccl_3(OH)_2$] :

■ **Actions:** • N. sedative • Hypnotic • G. anesthetic

■ **MOA:** it is reduced in the liver by non- microsomal enzymes into trichloroethanol which produce a direct depressant effect on CNS.

■ **Disadvantages :** • Narrow safety margin • Irritant drug and can cause tissue necrosis • Must be freshly prepared and diluted • Overdose causes respiratory failure and hypotension • It have no analgesic effect

Uses of Chloral hydrate in animals:

1- in ruminants given orally with linseed oil for treatment of flatulent colic 2- in horses used as a nerve sedative or general non volatile anesthetic
3- in dogs, it given with bromides to reduce convulsions in cases of epilepsy and strychnine poisoning

Bromides: Include Na+, K + and ammonium salts.

- They act as a nerve sedative by replacement with chloride ions in the extracellular fluid of nerve cells, so decrease chloride ions concentration and cause sedation. Bromides are used for treatment of epilepsy and strychnine poisoning. For dogs, they are used as anaphrodisiac to suppress sexual hyperexcitability

(2)Tranquilizers (Ataractics, Neuroleptics)

■ **Definition:** Are drugs, which relieve anxiety (insomnia) and mental tension in man. In animals, they produce calming effect and reduce fear so they are used :

(1) To calm vicious animals to facilitate their handling during clinical examination.

(2) Before transportation of animals for a long distance as they reduce fear and so avoid loss in body weight.

(3) As a preanesthetic to prolong the duration of volatile anesthetics.

(4) As a growth promoter for poultry as they quiten the birds.

■ **MOA:** They inhibit the metabolic enzymes as cytochrome oxidase in neurons and interfere with the utilization of ATP so decrease the activity of CNS.

■ **Examples:** Chlorpromazine (largactil), Hydroxyzine (atarax), Meprobamate (quitan), Promazine, Acepromazine, Azaperone and Reserpine.

(3) Anticonvulsants

- **Definition:** Are drugs which reduce or abolish **convulsions** that result by stimulation of spinal cord or motor area of the cerebral cortex.
- **Classification:**

1- Non Specific: e.g. • G. anaesthetics • barbiturates • xylazine • gallamine • tubocurarine

2- Specific: e.g. • phenytoin • primidone • sodium valproate • clonazepam • ethosuximide • mephenisin

- They depress the motor area in the brain and used for **epilepsy** in man and canine **distemper** in dogs.

- The central SK. M. relaxants (mephenesin) block the spinal transmission so abolish **tonic convulsions** and used for the treatment of **strychnine poisoning.**

Types of Convulsions

Types	Caused by	Treated by
Epileptic	⬆ of motor area of Cerebral cortex by toxic dose of caffeine	Phenytoin Sod. valporate Barbiturate
Clonic	⬆ of motor area of Cerebral cortex by toxic Dose of picrotoxine	Diazepam
Tonic	⬆ of spinal cord by toxic dose of strychnine	Barbiturate Bromides Mephenesine
Tetanic	By toxins of Clostridium tetani	Antitetanic serum

(4) Hypnotics

- **Definition:** Are drugs which produce **normal** sleep. In large dose, some hypnotics produce **deep** sleep and called **narcotics**.
- They cannot produce sleep if sleeplessness is due to **pain** because they have **no analgesic effect**.
- They are commonly used as **preanaesthetic** to reduce the amount of anaesthetic and prolong the duration of anaesthesia.
- **Examples:**

1- Xylazine (Rompun)

2- Chloral hydrate

Examples of hypnotics are:

(1) **Xylazine (Rompun):** is an organic base freely soluble in water and given by i.m. or i.v.

- It acts as a **sedative hypnotic** and possesses **analgesic** (unlike to chloral hydrate) and **skeletal muscle relaxant** effects. It acts by activation **of** α**2-receptors in CNS** as administration of α2 blockers (idazoxan) block xylaxine effects **(unlike to chloral hydrate)**.
- Xylazine is used to calm vicious animals before clinical examination and for treatment of spasmodic colic and skeletal muscle convulsions in all animals.
- Its side effects in dogs and cats: are **emesis** and **hypertension** and in horses are: **sweating, failure of respiration and hypotension**.

Differences	Chloral hydrate	Xylazine
Irritability	More	Less
Analgesic effect	NO	Yes
G. Anesthetic Effect	Yes	NO
MOA	Reduction to Trichloroethanol	Activation of α 2- receptors in CNS
Side effects	In dogs& cats : emesis and hypertension In horses: Sweating, failure respiratory and hypotension.	In dogs& cats : emesis and hypertension In pregnant cattle: Premature labour In horses : sweating

(2) Barbiturates

- All are derivatives of barbituric acid and their sodium salts are freely soluble in water. They have a gradual degree of depression to CNS from sedative hypnotics to G. anaesthetics. They are good skeletal muscle relaxant, but lack analgesic effect.

MOA:

They act by interfering with ATPase in the neurons of cerebral cortex so prevent the utilization of ATP by the cells and depression occurs.

Uses:

1-For induction of G. anesthesia as preanesthetic
2-For treatment of strychnine poisoning in dogs
3-For treatment of epilepsy and canine distemper
4-For intestinal colic as intestinal antispasmodic

Classification of Barbiturates

Class	Examples	Time of sleep
Long acting barbiturates	Phenobarbital sodium (Luminal) Barbital sodium (Veronal)	12-24 hrs Rarely used due to cumulative effect
Medium acting barbiturates	Amobarbital sodium (Amytal) hexabarbital sodium (Ortal)	6-12 hrs
Short acting barbiturates	pentobarbital sodium (Nembutal) secobarbital sodium (Seconal)	2-4 hrs
Ultra short acting barbiturates	hexobarbital sodium (Evipan) thiopental sodium (Nesdonal)	¼ -2 hrs

Toxicity and Treatment of Barbiturate Poisoning

Toxicity

1- Respiratory depression
2- Weak pulse
3- Low body temperature
4 - Coma
5- Death

Treatment

By administration of analeptics as:

1- Bemegride
2- doxapram
3- nikthamide

every 15-30 min. till recovery occurs

(5) Preanaesthetic Medication

■**Definition:** Are drugs which given **before** general anaesthetics to make it **more safer** and **agreeable** to the animal. They **reduce** **toxicity** or side effects of the anesthetic and insure **complete**

Group	Indication
I- Hypnotics, tranquilizers and analgesics	To produce **basal narcosis** (deep sleep) so reduce the amount of anesthetic required and it becomes **more safer**
II- Atropine or other Parasympatholytics	1- To reduces or prevents **salivary and bron. gland secretions** so prevents asphyxia or postoperative **drenching pneumonia** 2- To stimulate the **heart rate** 3- To stimulate **respiration rate**
III- Skeletal muscle relaxants	To produce **complete SK. M. relaxation** to facilitate **suturing** after surgical operation

Classification of Sk.M. Relaxants

Class	Example	Duration (MIN.)
Ultra short, Depolarizing	Succinylcholine	5 - 8
Short, Competitive	Mivacurium	12 -18
Intermediate, Competitive	Atracurium Vecuronium	30 - 60 60 - 90
Long, Competitive	Tubocurarine Doxacurium Pancuronium	80 - 120 90 - 120 120 - 180

(5) General Anaesthetics

■ **Definition:** Are drugs which produce complete loss of body movement, consciousness, sensation and reflexes by depressing the brain and spinal without interfering with the vital centers in medulla.

■ **An ideal anaesthetic should be:**

1- Easily administered
2- Non irritant
3- Cause rapid induction and short recovery periods
4- Good analgesic
5- Good skeletal muscle relaxant
6- Have a wide safety margin

■ **Theories of anaesthesia:**

1- Lipid solubility theory (Overtone-Mayer theory):

The anaesthetic drug must be soluble in lipids of CNS and the greater its solubility in fat than in water the more powerful its anaesthetic effect.

2- Surface tension theory:

The anaesthetic drugs lower the surface tension of nerve cells in CNS and prevent arrival of nerve impulses.

■Theories of Anaesthesia:

3-Colloid theory:

The anaesthetic drug causes aggregation of colloidal substances in the neurons of CNS so prevent or reduce neuronal transmission and anaesthesia occurs.

4- Cell permeability theory:

The anaesthetic drug decreases the permeability of membrane of the nerve cells so decrease the cell metabolism.

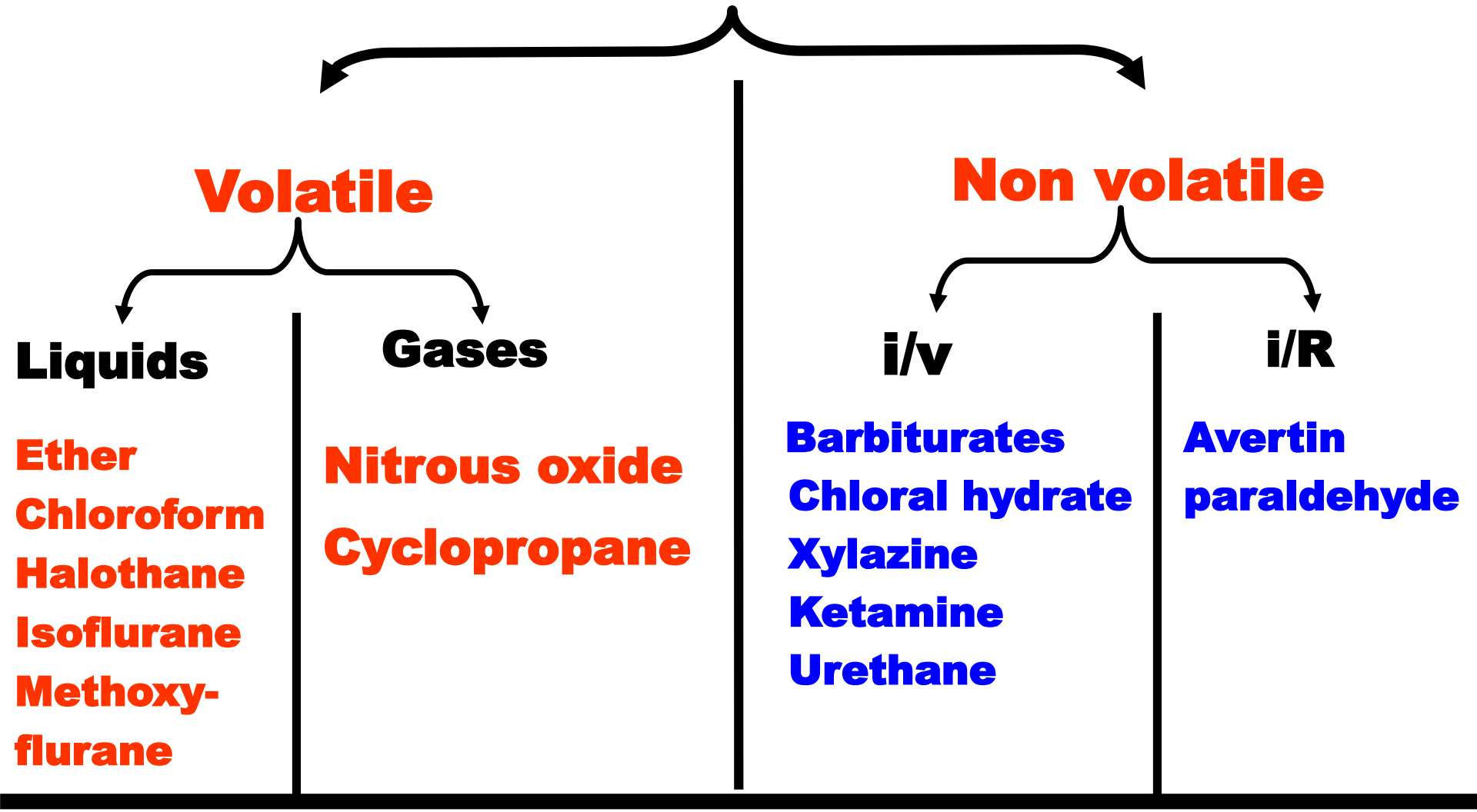
5- Neurophysiologic theory:

The anaesthetic drug prevents the neuronal transmission in the reticular formation of the brain, so prevent the arrival of impulses to other parts of the brain.

6- Biochemical theory:

The anaesthetic drug inhibits some metabolic enzymes as ATPase so inhibits carbohydrate metabolism and reduces energy which required for the activity of the neurons.

Classification of G. Anaesthetics



■ Methods of administration of volatile anaethetics

1- Open method (auto-inhalation method)
2- Closed method (positive feed method)

Common Properties of G.Vol. Anaesthetics:

1- Given by **inhalation,** inhaled with the inspired air and excreted with the expired air.

2- Produce **4 stages of anaethesia**: **(a)** Struggling **(b)** Narcotic **(c)** Anaethetic (Light, Medium & Deep) **(d)** Paralytic or Recovery.

3- Produce **rapid** induction and recovery periods .

4- Some of them are **irritant** (chloroform) , others are **inflammable** (ether) and others **lack analgesic** effect (Halothane) .

Difference	Volatile Anaethesia	Non volatile Anaethesia
Administration	By inhalation	By injection
Struggling stage	Present	Absent
Induction period	Short	Relatively long
Recovery period	Short	Relatively long
Excretion	In expired air	In urine

Differences	Ether	Chloroform
Chemical structure	C2H5-O-C2H5	CH cl3
Melting point	35 Ċ	61 Ċ
Physical properties	Inflammable, explosive	Non inflammable, non explosive
Irritant effect	More + +	Less +
Anaesthetic effect	Less +	More + + + +
Induction period	Long + +	Short +
Recovery period	Long + +	Short +
Sk. M. relaxant effect	Less +	More + +
Concentration used	Induc: 5–15% Main: 2.5 – 7.5 %	Induc: 1–3% Main: 0.5 -1.5 %

Halogenated Ethane Derivatives

Halothane

Volatile colorless liquid,
Non irritant to M Membranes
More powerful than chloroform
More myocardial and respiratory depressant effect

Isoflorane

Volatile colorless liquid,
Non irritant to M Membranes
Potent as anaesthetic as ether
Less myocardial and respiratory depressant effect

Differences	Nitrous oxide	Cyclopropan
Packing	In blue cylinders	In orange cylinders
Physical Prop.	Inflammable, explosive	Non inflammable, Non explosive
Anaesthetic effect	Moderate as ether	More as chloroform
Respiratory& heart depression	Less toxic	More toxic

Common Properties of Non Volatile Anaesthetics:

- **Given by injection:**

1- Chloral hydrate → I/V 2- Avertin → I/R

3- ketamine → I/M or I/V 4- Urethane → I/P

- **No struggling stage**
- **Metabolized in the liver and almost excreted in the urine**
- **They are non irritants to M. membranes**
- **Some of them lack analgesic activity**
- **Others produce incomplete skeletal muscle relaxation**

Animals	Anaesthetic	Route
Calves	Halothane + analgesic	Inhalation
Cattle	Barbiturates + local anaesthetic	Injection
Horses	Chloroform, Chloral hydrate	Inhalation i.v.
Sheep& goats	Cyclopropan Barbiturates	inhalation Injection
Dogs	Barbiturates Ketamine + Xylazine	i.v. or i.m i.v. or i.m
Cats	Ketamine + Xylazine Alphaxalone	i.v. or i.m i.v. or i.m
Rabbits	Urethane Chloralose	i.v. i.v.

(6) Local Anaesthetics

■ **Definition:** Are drugs which produce temporary loss of sensation and reflexes at site of application due to temporary paralysis of the sensory nerves.

■ **Properties of an ideal local anaesthetic:**

1- Should be water-soluble and stable in its solution

2- Non irritant to tissues and non-toxic

3- Slowly absorbed to produce a prolonged effect

4- Produce its effect in small concentrations

5- Cause rapid and prolonged effect

■ **Classification:**

I- According to the mode of action:

1- Acting physically (by freezing):

e. g. (a) Ethyl chloride (b) Compressed CO_2 gas

When they are sprayed on the skin they are rapidly evaporated and cause severe cooling which cause temporary paralysis of the sensory nerves and local an aesthesia occurs.

2- Acting chemically:

e.g. Procaine(Novocain), Amethocaine, Benzocaine, Butacaine, Lidocaine and Cinchocaine

When they are applied on the M. membranes or injected by infiltration, they inhibit Na+ ions transport through the membrane of nerve cells (inhibit sodium pump), so inhibit transmission of impulses and local anaesthesia results.

■ Uses of physically acting anaethetics:

1- Opening of abscesses.

2- Removal of warts.

3- Removal of broken claw.

■ Uses of chemically acting anaethetics:

1- For operation of cornea (corneal Anesthesia) in dogs

2- For diagnosis of lameness in horse (N. block Anesthesia)

3--For surgical operations in hind limbs, tail and udder(Anterior epidural An) ruminotomy and cesarean(Posterior epidural An.) in ruminants

II- Classification According to Method of Application

1-Topical (Surface): The anaesthetic is applied on the surface of skin or m.m of eye, nose, anus and urethra e.g. ethyl chloride spray on skin or as sol., oint. or paste (Butacaine, Lignocaine, Amethocaine).

2-Local infiltration (Field): The anaesthetic is injected intradermally or S/C around a local area of skin, so the infiltrated area can be incised without pain. e.g. Procaine Hcl (Novocaine) local infiltration in G.pig.

3-Nerve block (Regional): The anaesthetic is injected near a main nerve trunk to anaesthetize the region that is supplied by this trunk e.g.

1- Sciatic nerve blocks anaesthesia in frog by amethocaine. 2- Volar nerve block anaesthesia in horse by procaine for diagnosis of lameness.

4-Epidural anaesthesia:

(a) Posterior epidural anaesthesia: A small dose of the anaesthetic is injected in epidural space between coccygeal vertebrae. This type is used in ruminants for surgical operations in hind limbs, tail and udder.

(b) Anterior epidural anaesthesia: The dose of anaesthetic is increased so a large region becomes anaesthetized. This type is used for ruminotomy and cesarean in ruminants.

N.B.: (1) Procaine is not suitable for surface (topical) anaesthesia because it not absorbed from skin and mucous membranes. (2) Procaine is usually combined with adrenaline to prolong its duration of action because adrenaline constricts the cutaneous blood vessels so delay absorption of procaine.

(7) Analgesics = Antinociceptives

■ **Definition:** Are drugs which relieve or abolish **perception of pain** by depressing the pain center in thalamus without seriously impairing consciousness.

■ **Classification**

I- Narcotic analgesics
= Opiate analgesic
= Morphine - like drugs

1- Morphine (Opium alkaloids)
2- Morphine derivatives
3- Morphine substituents

II- Antipyretic analgesics
= Non opiate analgesics
= Aspirin - like drugs

1- Salicylic acid derivatives
2- Aniline derivatives
3- Pyrazolone derivatives
4- Modern NSAIDs

I- Opiate Analgesics

■ **Opium:** It is the dried milky exudates of the unripe fruits of poppy plant (*Papaver somniferum* plant). The exudates contain many alkaloids known as opium alkaloids, which are classified according to their chemical structure pharmacological properties into: phenanthrene and isoquinoline derivatives.

Type	Alkaloids	%	Pharmacological properties
Phenanthrene derivatives	Morphine Codeine Thebaine	10.0 0.5 0.2	1-Analgesic 2-Addictive 3-Spasmogenic
Isoquinoline derivatives	Papaverine Narcotine	1.0 0.6	1-Non analgesic 2-Non addictive 3-Spasmolytic i.e. Non spasmogenic

■ Morphine

■ Actions :

1-On CNS: differ according to species:

- **In man and dog** → 1st stimulation (euphoria) followed by depression and sedation
- **In horse, cattle & sheep** → short period of excitement followed by depression and sedation
- **In cat** → excitement without depression(Not used)

2-On Medullary centers:

- ↑ Vagal & Vomiting C, But ↓ Cough& Respiratory C

3-On GIT:

- ↑ intestinal motility via vagal center Stim. (Centrally)
- Contract GIT sphincters and ↓ Intestinal motility (directly)

▫ The net result is initial defecation followed by constipation.

4- Addictive action: In man is a serious social problem as the addict become tolerant and dependant on morphine.

N.B. : The addict is characterized by pin pupil & constipation

■ MOA of morphine as narcotic analgesic:

by acting on subtype M opoid (μ,δ, κ,σ) receptors in cerebral cortex and thalamus producing analgesia with hypnosis.

■ Uses or indications of morphine:

1- As preanaesthetic to reduce pain due to its analgesic effect
2-For treatment of spasmodic colic due to it spasmolytic effect.

■ Morphine antagonists:

Are competitive antagonist for opoid receptors that antagonize morphine effects and used for treatment of morphine poisoning. They are:

1-Partial antagonists ⟶ produce antagonist with slight agonist activity as Nalorphine & Pentazocine
2-Total antagonists ⟶ produce complete antagonist activity as Naloxone and Naltrexone

■ Morphine Derivatives:

1- Codeine:

One of opium alkaloids of phenanthrene derivative It has similar effects as morphine, but it is less toxic, less potent as analgesic (1/10 potency of morphine) and less potent as cough and respiratory depressant (¼ potency). It is used as phosphate for treatment of dry cough in dogs and as analgesic and cough sedative in man.

2- Apomorphine Hcl:

It is one of morphine derivatives. Its effect on CNS is similar to morphine but it is less potent. It is used for induction of emesis in dogs (central emetic) as it stimulates CTZ and vomiting center after its S/C injection.

■ Papaverine:

- One of opium alkaloids of isoquinoline derivatives
- Has NO effect on CNS
- It acts as a smooth muscle relaxant
- differs from morphine as it is non analgesic, non addictive and non spasmogenic (but spasmolytic)
- Used for treatment of colic (intestinal, renal and biliary) , bronchial asthma and hypertension.

■ Morphine substituents:

- Are a group of recent drugs which produce similar effects as morphine.
- Less potent than morphine and their effects is short due to their rapid metabolism.
- Examples: Methadone, Pethidine, Etorphine Fentanyl , Alfentanyl and Sufentanil.

II- Non Opiate Analgesics

- **Definition:** Are drugs which **reduce pain** and **lower the abnormal rise of body temperature** so used for fever, headache and rheumatic pain.

Classification

Class	Example
Salicylic acid derivatives	Acetylsalicylic acid (Aspirin), Sodium salicylate
Aniline derivatives	Phenacetin - Acetanilide Paracetamol
Pyrazolone derivatives	Phenylbutazone - Phenazone Dyperone (Novalgin)
Modern NSAIDs	Meclophenamic A – Mephenamic A Ketoprofen – Ibuprofen – Naproxen

1- Salicylates

- Are used in medicine since many years ago as scales of Willow plant which contain " Salicin " as an active substance.
- Salicylic acid is only used locally (because it is irritant) as Keratolytic, antiseptic and fungistatic for mycotic infections.
- Salicylic acid derivatives as sodium salicylate and methyl salicylate are water soluble, but acetyl salicylic acid (aspirin) is sparingly soluble in water.
- Methyl salicylate is used as a counter irritant (as liniment) for chronic arthritis .
- Salicylates and aspirin are used as antipyretic analgesics for fever, pain, headache and rheumatic pains.

■ Actions and MOA of Salicylates:

1-Antipyretic by:

(a) Inhibiting heat-regulating center in hypothalamus

(b) Causing peripheral vasodilatation so increase heat loss through sweating & lower B. temperature

2-Analgesic by:

Preventing arrival of pain impulses between sensory area of cerebral cortex and thalamus (Pain Center)

3-Antiinflammatory by:

(a) Inhibiting of cyclooxygenase enzyme (Cox1) which is necessary for synthesis of prostaglandins (PGs) that are responsible for inflammation, pain and fever.

(b) Stimulating adrenal cortex to secret glucocorticoids

2- Aniline Derivatives

1- Phenacetin and Acetanilide: have the same effects of salicylates except the anti-inflammatory effect. They are metabolized into acetaminophen which depresses pain and heat regulating centers so they act as antipyretic analgesics. Their toxic effects include liver and kidney damage, hemolytic anemia and hypoxia in blood due to oxidation of HB beside some additive properties so they are rarely used now.

2- Paracetamol: is less toxic than phenacetin and acetanilide and free from side effects of aspirin. It is used as a potent antipyretic analgesic for fever and pain.

3- Pyrazolone Derivatives

1- Phenazone and phenylbutazone:

act as antipyretic, analgesic and anti-inflammatory and used for chronic rheumatism. They also increase the excretion of uric acid in urine (uricosuric effect) so they are useful for gout.

2-Novalgin (dyperone):

is commonly used for muscular rheumatism, sciatica and neurlgesia as it act as antipyretic, analgesic and anti-inflammatory

4- Modern NSAIDs

The most widely used drugs for inflammations (inflammatory joint diseases). They include many drugs as naproxen, ibuprofen, ketoprofen, indomethacin, meclofenamic acid. They produce antipyretic, analgesic and anti-inflammatory effects by inhibition of cyclooxygenase enzyme. They are used for acute and chronic arthritis, toothache, dysmenorrheal pain, cancer pain and rheumatoid arthritis.

Differences	Narcotic Analgesics	Antipyretic Analgesics
Example	Morphine	Aspirin
Antipyretic Effect	NO	Yes
Hypnotic Effect	Yes	NO
Addictive effect	Yes	NO
Anti-inflammatory	NO	Yes
Analgesic effect	More	Less
Types of pains	All types	Mild + Moderate
Resp. and cough depressant effect	Yes	NO
Toxicity	High	Relatively Low


ThanK YOU