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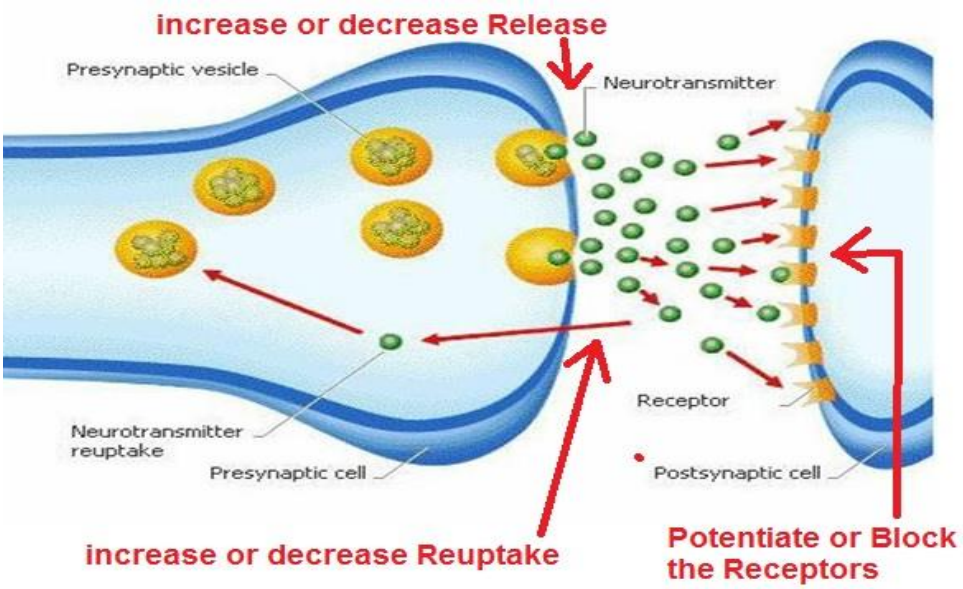
Drugs acting on the Central Nervous System (CNS)

The CNS is consisted of the brain and spinal cord. The brain composed of the cerebrum, cerebellum and medulla oblongata.

Neurotransmitters

Neurotransmitters are biological substances that transmit signals from a presynaptic neuron to a target receptor on the postsynaptic neuron.



(General Mechanisms of the Drugs that acting on the CNS)

Types of neurotransmitters in the CNS:

1. Acetylcholine (Ach).

2. Catecholamines that composed of Norepinephrine (NE), Epinephrine (Epi) and Dopamine (DA).

3. Serotonin (5-hydroxy tryptamine)(5-HT).

4. Aminoacids that divided into:

A. Inhibitory (GABA and Glycine).

B. Excitatory (Aspartate and Glutamate).

Sedatives and Hypnotics

Hypnotics are drugs that cause hypnosis by depressing the CNS so the animal is less responsive to external stimuli. Hypnotics that used in small doses will cause sedation.

Types

Barbiturates

Divided into:

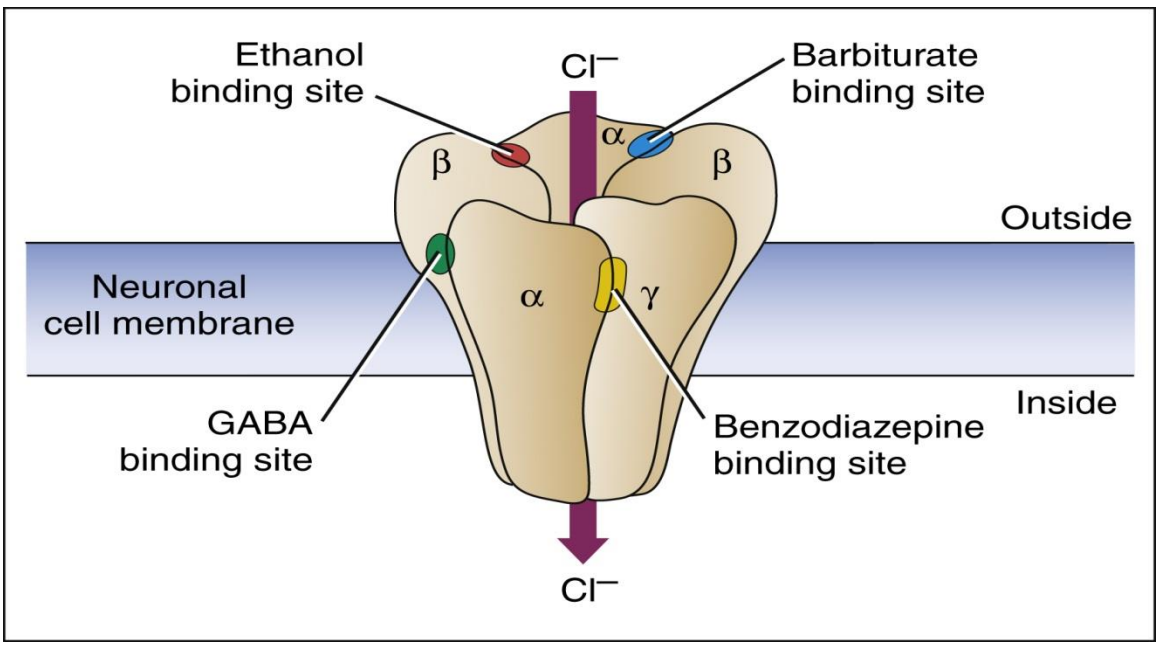
A. Long acting (Phenobarbital).

B. Short acting (Pentobarbital).

C. Ultra-short acting (Thiopental).

Mechanism of action

Potentiate the effect of GABA neurotransmitter leading to depression of the brain and inhibits excessive motor discharge.



Pharmacological effects

1. Depresses all functions of the brain.

2. Selectively depresses the motor cortex.

3. Depresses the respiratory center in medulla.

4. Produce good muscle relaxation.

5. Decreases blood pressure and heart rate.

6. Induce microsomal enzymes and increase the metabolic rate of the animal.

Clinical uses

1. Sedative.

2. Hypnotic.

3. Anticonvulsant.

4. Anesthetics.

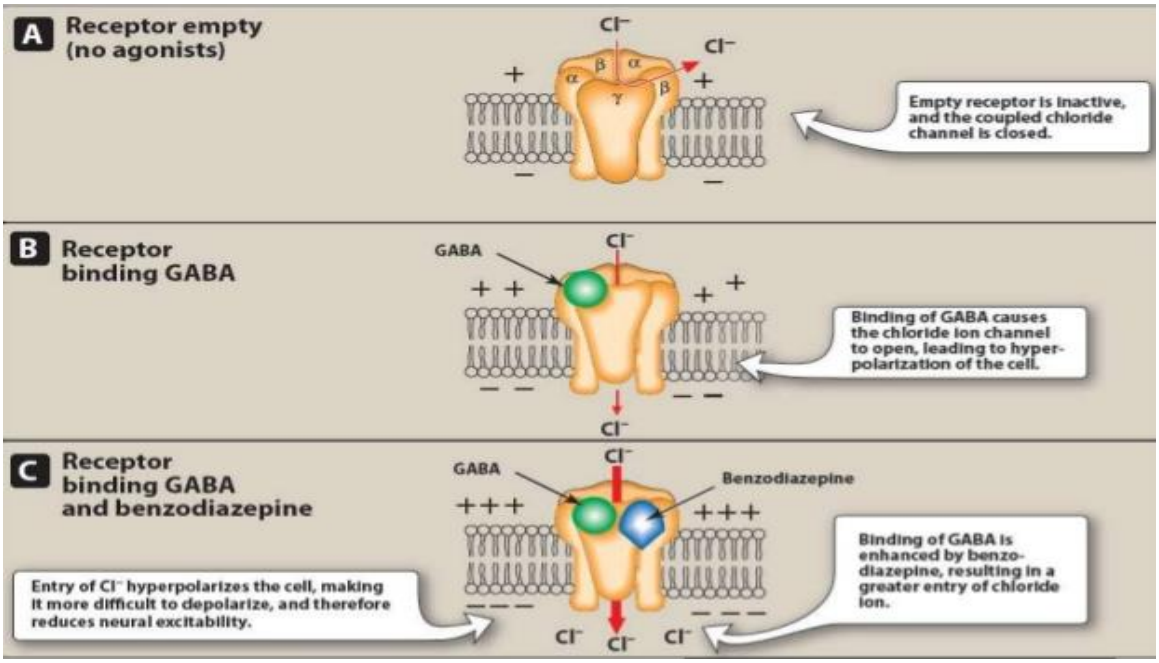
5. In case of pruritus to control itching.

Benzodiazepines

Which include diazepam, chlordiazepoxide and alprazolam.

Mechanism of action

Increasing the action of GABA neurotransmitter on its receptor which causes influx of chloride ion into the neuronal cells leading to depression of the CNS.



Clinical uses

1. Sedative.

2. Hypnotic.

3. Muscle relaxant.

4. Anticonvulsant.

5. Preanesthetic.

6. Antianxiety.

Chloralhydrate

It is hypnotic given I.V. in large animals (7%). It depresses the respiratory and vasomotor centers. It is metabolized in the body by reduction into Trichloroethanol which is the active metabolite responsible of hypnotic effect of chloral hydrate. It is used as anesthetic in equine species with weak analgesic effect and can be mixed with Magnesium sulfate (MgSO4) (6%) to produce muscle relaxation. Chloral hydrate decreases blood pressure and decreases heart rate and sudden death may occur in horses which are highly excited.

Ethanol

It has sedative effect, depresses respiration and causes vasodilation. It has diuretic effect because it inhibits antidiuretic hormone (ADH). It metabolized into CO_2 and H_2O and small amount expired by the lungs.

Anticonvulsant Drugs

Are drugs used to control seizure through depressing the CNS.

Types

Barbiturates

Benzodiazepines

Phenytoin

Mechanism of action

It stabilizes the neuronal membranes and selectively depresses the motor areas in the brain.

It is not hypnotic, well absorbed orally, induces liver microsomal enzymes, metabolized in the liver and excreted in the bile.

Side effects

1. Transient incoordination.
2. Polyphagia.
3. Polyurea.

Primidone

The structure of this drug and its mechanism of action is similar to phenobarbital and about 25 % of the drug is metabolized into phenobarbital. It causes nausea, ataxia and not used in cats because it causes neurotoxicity.

Narcotic Analgesics

Are drugs used to produce analgesia through its action on the CNS.

Opioids agonists

Types

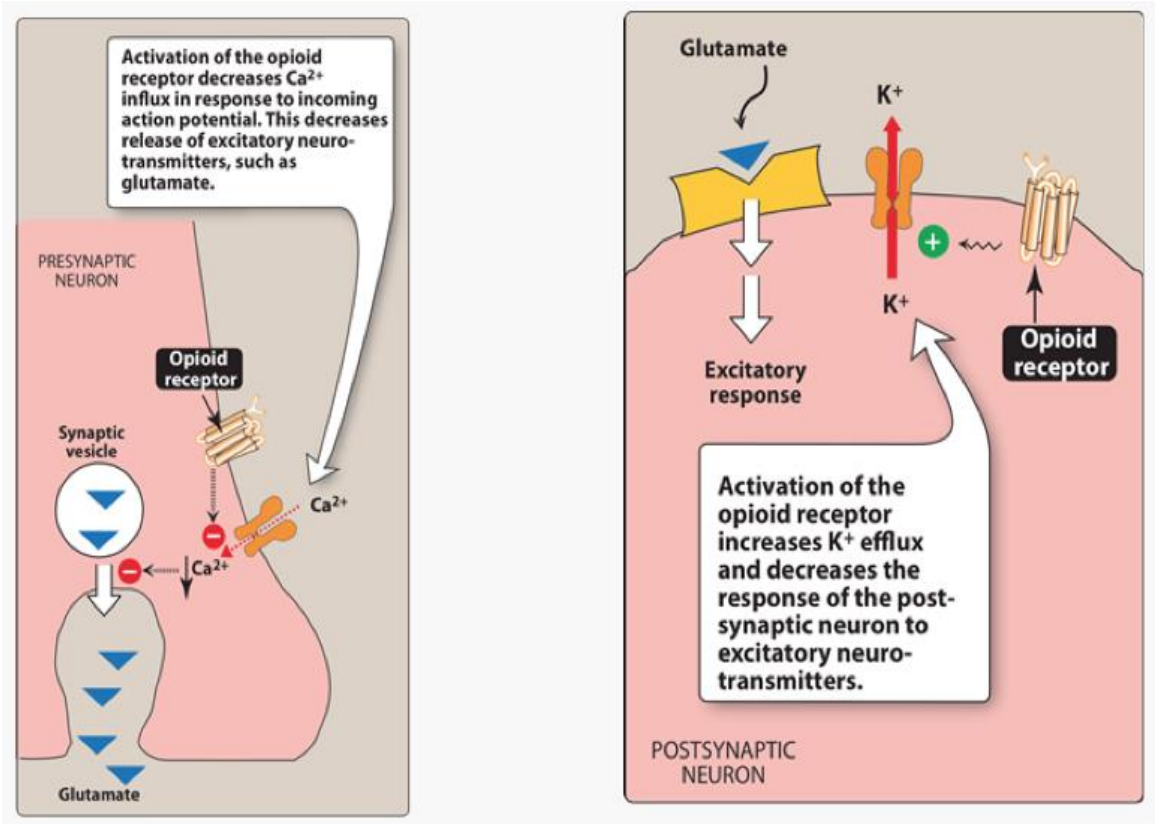
1. Natural like Morphine.

2. Synthetic like Fentanyl.

Morphine

Mechanism of action

It acts on opioid receptor (Mu receptor) in the CNS leading to depression of the brain and causing analgesia.



Pharmacological effects

A. On the brain:

1. Depresses the brain in dogs, monkey and human but it causes CNS excitation in cats, horses and ruminants.

2. Produces analgesia by increasing the pain threshold.

3. Produces euphoria in human.

4. Stimulates the Chemoreceptor Trigger Zone (CTZ) in the brain leading to emesis in dogs.

5. Depresses the cough center.

6. Depresses the respiratory center in the brain.

B. On the GIT:

The initial dose of morphine causes defecation but chronic use causes constipation.

C. On the skin:

Morphine causes itching because of histamine release.

Clinical uses

1. Analgesic.

2. Preanesthetic.

Contraindications

1. In case of shock because morphine causes respiratory depression.

2. In case of liver diseases.

3. In case of pulmonary edema.

Toxicity

Death may result from respiratory depression and it can be treated by giving opioid receptor antagonist like Naloxone.

Tranquilizers

Are drugs used to tranquilize and control of the animals and they are called also Neuroleptics.

Phenothiazine derivatives

Types

Chlorpromazine, Acepromazine and Promazine.

Chlorpromazine

Mechanism of action

They antagonize dopamine receptors in the brain leading to depression of the CNS.

It also has anticholinergic and antiadrenergic effects.

Clinical uses

1. Control the nervous animals.

2. Preanesthetic.

3. Antipruritus.

4. Antiemetic.

5. Antistress in transporting of animals.

Side effects

1. Incoordination in horses.

2. Dry mouth.

3. Constipation.

4. Hypotenstion.

5. Decreases body temperature.

CNS Stimulants

Methylxanthines derivatives

Types

Caffeine, Theophylline and Aminophlline.

Mechanism of action

Antagonism of adenosine receptors in the brain leading to CNS stimulation.

Pharmacological effects

1. Stimulates CNS, decrease fatigue and increases motor activity.

2. Stimulate the heart and causes vasodilation.

3. Relaxation of smooth muscle therefore theophylline is used in asthma.

4. Diuretic effect through increasing renal blood flow.

5. Stimulation of gastric acid secretion.

Amphetamine

Mechanism of action

It increases the release of Norepinephrine and Dopamine from the nerve endings leading to CNS stimulation.

Medullary Stimulants

Doxapram

Mechanism of action

It stimulates the respiratory center in the medulla and causes respiratory stimulation.

Clinical uses

1. Antagonizes the respiratory depressant action of Barbiturates.

2. Antagonizes the sedative action of xylazine.

Pentylenetetrazole

It is a respiratory stimulant. It increases respiration. High doses produce convulsion and it is used as respiratory stimulant.

4-aminopyridine

It is used as respiratory stimulant and antagonizes the sedative effect of xylazine.

Nikethamide

It is a short acting respiratory stimulant.

Spinal Cord Stimulants

Strychnine

Mechanism of action

Antagonizes glycine receptors in the spinal cord.

Indications

1. Improves appetite in very small quantity.

2. Used as tonic.

3. Kill the stray dogs.

Anesthetics

Anesthetics are drugs that used to induce anesthesia in whole body (general anesthetics) or local area of the body (local anesthetics). It is divided into:

1. General Anesthetics

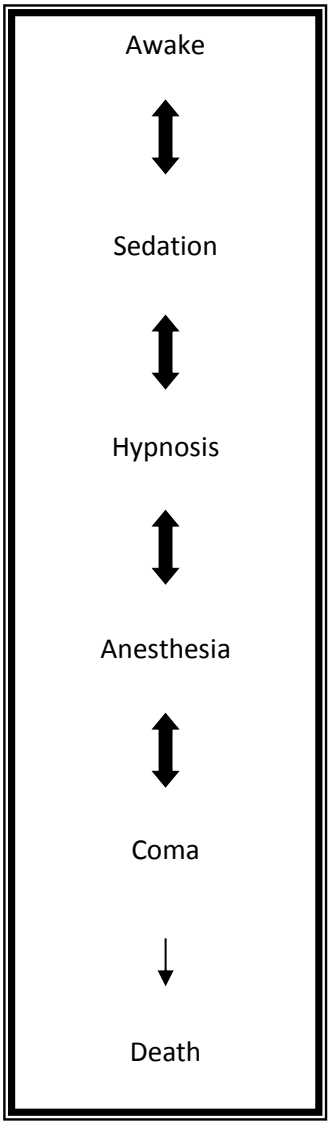
A. Inhalational Anesthetics

B. Injectable Anesthetics

2. Local Anesthetics

1. General Anesthetics

Drugs used to induce general anesthesia which is characterized by loss of sensation that achieved by reversible depression of the brain.



Clinical characteristics of general anesthesia:

1. Loss of sensation.
2. Unconsciousness.
3. Muscle relaxation.
4. Inhibition of reflexes.

Ideal anesthetics:

1. Nonirritant and without bad odor.
2. Potent with smooth induction and recovery.
3. Wide margin of safety.
4. Good muscle relaxation.
5. Does not damage the CNS with minimal side effects.

6. Inexpensive and non-explosive.

7. Ease of administration.

Routes of general anesthetics administration:

1. Inhalation.

2. Intravenous (I.V.).

3. Intramuscular (I.M.).

4. Subcutaneous (S.C.).

5. Intraperitoneal (I.P.): Usually used in laboratory animals like mice and rats.

6. Intra-thoracic (I.T.): used for euthanasia of animals.

7. Orally (P.O.): is not recommended because it produces hypnosis and has long induction period due to first pass effect in the liver.

Stages of general anesthesia

Stage-I (stage of voluntary excitement, stage of analgesia):

It is characterized by struggling and ataxia without CNS depression.

Stage-II (stage of involuntary excitement, stage of delirium):

It begins with unconsciousness and loss of voluntary control.

Stage-III (stage of surgery, stage of anesthesia):

Characterized by unconsciousness, loss of neuromuscular reflexes, loss of pain sensation and muscle relaxation. All surgical operations can be performed at this stage.

This stage can be subdivided into 4 planes:

a. Sleep

b. Sensory loss

c. Muscle paralysis

d. Intercostal paralysis

The first two planes are called light surgical anesthesia and the last two are called deep surgical anesthesia.

Stage-IV (medullary paralysis):

Characterized by paralysis of the vital regulatory centers in the medulla like respiratory center and death may occur in this stage.

Notes:

-Stage I and II are called the induction period.

-Some anesthetics bypass stage II into stage III which is the stage of surgery (e.g. Halothane, Methoxyflurane and Barbiturates).

-Other anesthetic agents induce all the stages of general anesthesia (e.g. Ether and Chloroform) while some anesthetics produce only stage I and II (e.g. Ketamine, N_2O and Enflurane).

Characteristic features of balanced anesthesia:

1. Analgesia.

2. Muscle relaxation.

3. Hypnosis.

4. Hyporeflexia.

Preanesthetics (Premedications)

Preanesthetics used with general anesthetics to produce balanced anesthesia:

1. **Analgesics** like xylazine and morphine.

2. **Sedatives and hypnotics** like diazepam.

3. **Tranquilizers** like chlorpromazine.

4. **Muscle relaxants** like D-tubocurarine.

5. **Adrenergic blocking agents** like propranolol.

6. **Cholinergic antagonists** like atropine because of:

a. to reduce salivation.

b. to reduce bronchial secretion.

c. to prevent bradycardia.

A. Inhalational Anesthetics

1. Gaseous like N_2O and Cyclopropane.

2. Volatile like Halothane, Methoxyflurane, Enflurane and Ether.

Inhalational anesthetics are gases or vapors that diffuses readily across the pulmonary alveoli and then to the brain to produce anesthesia.

The transfer of inhalational anesthetics depends on the partial pressure of anesthetics and its solubility in the blood.

Lipid solubility is important for induction of anesthesia and recovery from it. High lipid solubility means long induction and long recovery periods of anesthesia (e.g. Ether) while low lipid solubility means rapid induction and fast recovery (e.g. Halothane).

General mechanisms of action of inhalational anesthetics:

1. Interaction with lipid molecules of the cell membrane.

2. Interaction with proteins of the neuronal membrane.

3. Interaction with water molecules of the cell membranes.

All general anesthetics causes stabilization of the cell membrane.

Minimal Alveolar Concentration (MAC):

It is the minimal concentration of the anesthetics at the alveolar level which is required to produce anesthesia in 50 % of the animals.

Halothane

It is nonirritant, nonflammable, non-explosive and potent. It depresses all the functions of the brain. It bypass stage II. It has rapid induction and fast recovery because it is low lipid soluble.

Side effects of Halothane:

1. Respiratory depression.

2. Depresses cardiac function.

3. Sensitizes the heart to catecholamines.

4. Decreases calcium ion binding to cardiac muscle and causes bradycardia.

Contraindication:

Uses of epinephrine and norepinephrine are contraindicated in case of halothane anesthesia.

Advantages:

1. It is potent and has rapid induction and rapid recovery from anesthesia.

2. It produces good muscle relaxation.

Disadvantages:

1. Cardio-pulmonary depression.

2. Expensive.

3. Contraindicated in cardiac diseases.

Methoxyflurane

It is more potent than halothane, it has long induction and long recovery periods. During recovery, there is some CNS excitation because of high lipid solubility so that, preanesthetics are needed.

Side effects:

1. Decreases heart rate and blood pressure.

2. Sensitizes the heart to catecholamines.

Advantages:

Potent with good muscle relaxation and analgesia.

Disadvantages:

1. High lipid soluble with long induction and long recovery periods.

2. It is contraindicated in liver and kidney diseases.

Nitrous oxide (N_2O)

It is colorless, odorless, nonirritant and nonflammable. It is usually given as 80% N_2O and 20% O_2. It produces stage I and II anesthesia. It produces good analgesia, muscle relaxant is needed and O_2 is given to prevent hypoxia. It is characterized by low lipid solubility so that, the induction and recovery from anesthesia is fast. It is used with other anesthetic because it has low potency.

Enflurane

It is potent anesthetics and structural analogue to Methoxyflurane. It is also sensitizes the heart to catecholamines. It produces good muscle relaxation and may cause CNS excitations.

Ether

It is flammable, highly explosive and used in laboratory animals. It causes respiratory irritation and produces all stages of anesthesia.

Chloroform

It is used in laboratory animals but causes liver toxicity so that, not used in other animal species.

B. Injectable Anesthetics

Advantages of Injectable anesthesia:

1. Minimal apparatus used.
2. Ease of induction.
3. Useful in head surgery.
4. Diminish the side effects of anesthetic in case of respiratory diseases, debility and shock.

Disadvantages of Injectable anesthesia:

1. The depth and the level of anesthesia cannot easily controlled.
2. Ease of occurrence of anesthetics overdose.

I. Barbiturates anesthetics

II. Non-barbiturates anesthetics

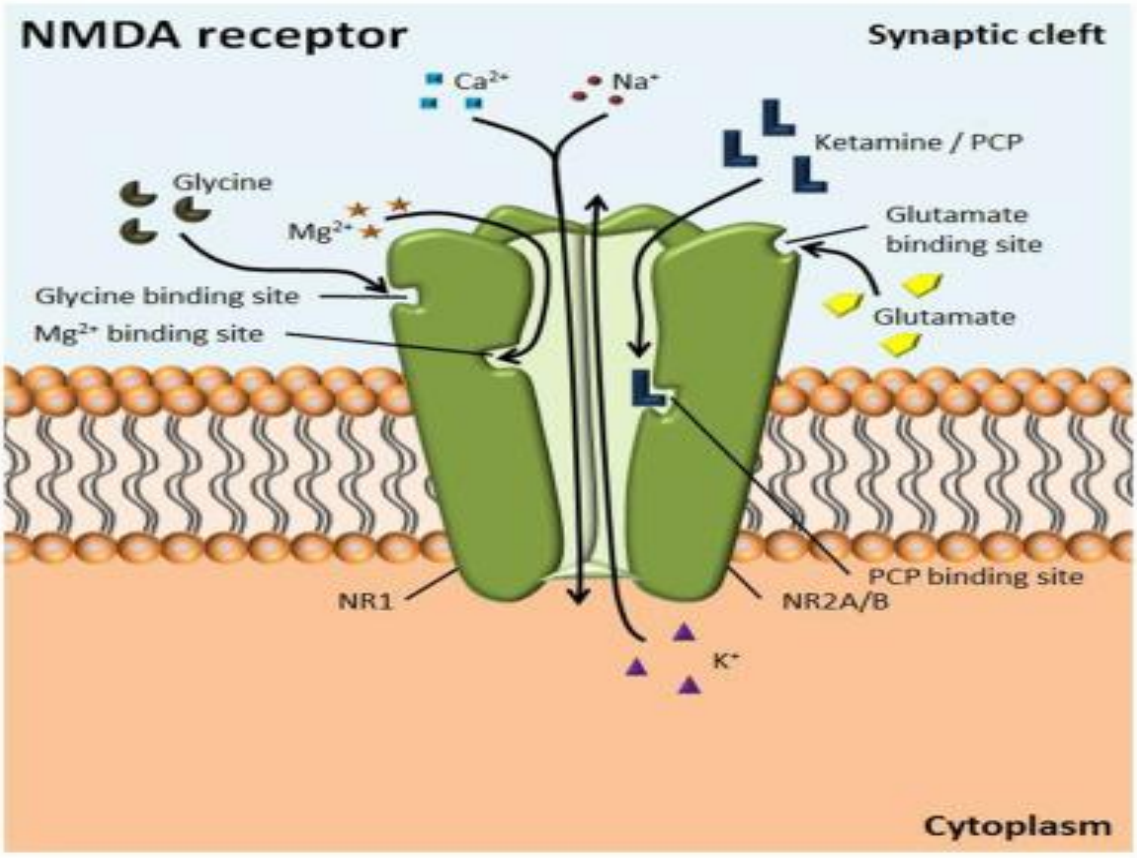
Ketamine

Mechanism of action:

Antagonizes aspartate receptors (N-methyl-D-aspartate (NMDA) receptors) leading to depression of the brain.

It is given I.M., I.V. and S.C. It produces stage I and II anesthesia with weak muscle relaxation therefore, it is usually combined with α_2 receptor agonists like xylazine, meditomidine and detomidine.

The analgesia is good and body reflexes like swallowing are maintained during ketamine anesthesia.



Contraindications:

1. Abdominal surgery.

2. Caesarian section (CS).

3. Liver and kidney diseases.

4. Head injuries because ketamine increases the pressure of cerebrospinal fluid (CSF).

Propofol

Mechanism of action:

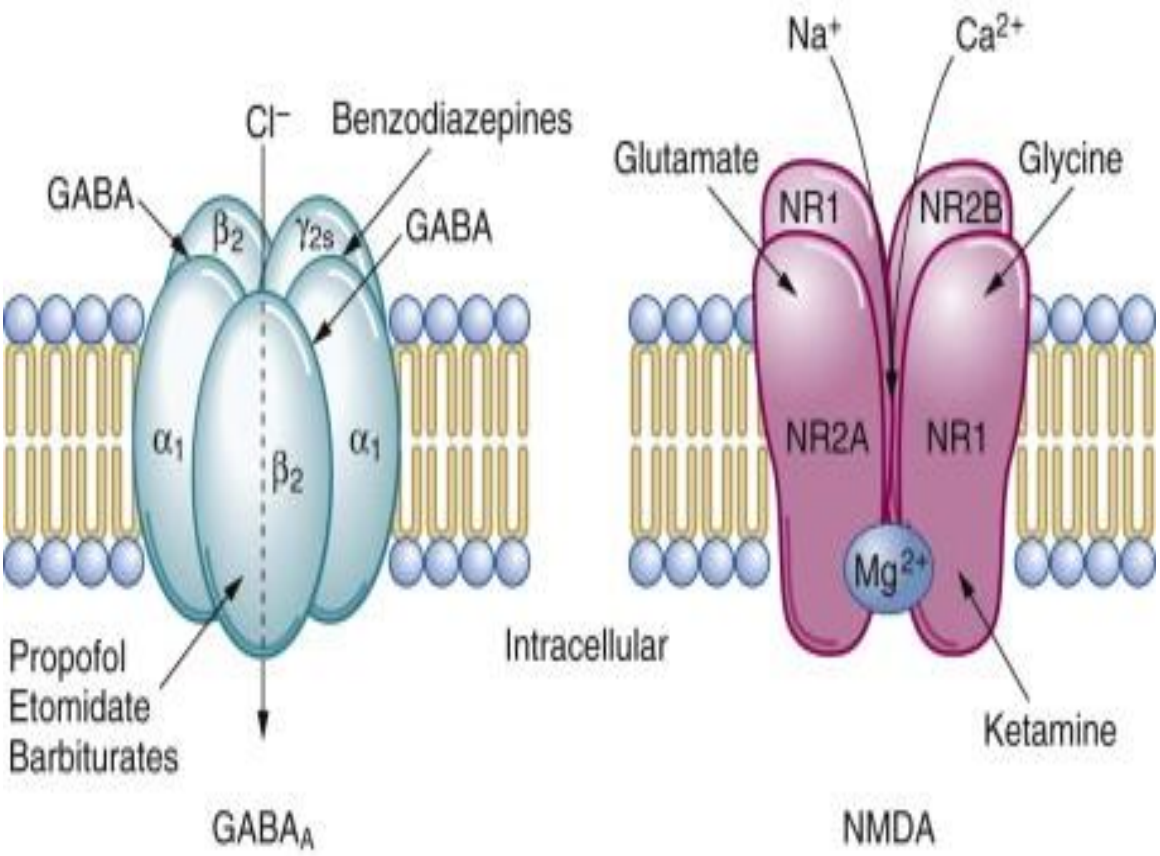
Potentiate the effect of GABA neurotransmitter leading to inhibition of the brain. It is usually used in dogs and cats and has rapid onset of action and short duration of anesthesia about 15-30 minutes. It produces good muscle relaxation but vomiting and hypotension may occur.

Etomidate

Mechanism of action:

Increases the effect of GABA neurotransmitter leading to inhibition of the brain. It is short acting I.V. anesthetic agent and has short duration about 3-5 minutes. It decreased corticosteroids production by suppression of the adrenal gland.

Chloralhydrate



2. Local Anesthetics

Mechanism of action of local anesthetics:

Local anesthetics prevents the local pain by blocking the sodium channel and reversibly prevent the depolarization of the nervous tissue.

It is injected at the site of action and it is called nerve block when it is injected around or close to peripheral nerve or nerve plexuses.

It is called epidural anesthesia when injected into the spinal cord spaces and do not interfere with the vital or local functions of the body.

The absorption of local anesthetics can be delayed by giving epinephrine which causes vasoconstriction that prolonged the duration of anesthetic action.

Types of Local Anesthetics:

1. Esters: e.g. Procaine and Tetracaine.

2. Amides: e.g. Lidocaine and Etidocaine.

Side effects:

1. Hypotension.

2. Urinary retention.

3. Difficulties with motor muscles.

4. Nausea and vomiting.

5. Seizure.

Clinical uses:

1. Relief of local pain.

2. Tail amputation in animals.

3. Insect bites.

4. Minor burns.

5. Local itching.

Local anesthesia induced physically

Ethyl chloride: is volatile liquid stored under pressure and released as a spray, it cools the skin and cause local anesthesia.

CO_2 ice: used to cauterize warts and induced local anesthesia.

References:

1. Hsu, W. H. (2008). Handbook of veterinary pharmacology. 1st ed., Wiley-Blackwell, USA.

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