general anesthetics

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Objectives

By the end of this lectures you should be able to:

1. Identify the main inhalation anesthetic agents and describe their pharmacodynamic properties and side effects
2. Describe the relationship of the blood: gas partition coefficient of an inhalation anesthetic with its speed of onset of anesthesia and its recovery time
3. List the factors that influence inhalation anesthetic biodisposition
4. Describe the main pharmacokinetic and pharmacodynamic characteristics of the intravenous anesthetics

General Anesthesia

General anesthesia is a reversible state of **unconsciousness** produced by anesthetic agents and characterized by **loss of the body sensations**, **analgesia** and **amnesia** and **skeletal muscle relaxation**.

It is used almost exclusively in surgery.

Used also in other painful invasive procedures.

No one anesthetic agent can produce analgesia, muscle relaxation, loss of body sensations and amnesia, **so:**

- A combination of agents (balanced anesthesia) is used in the three clinical phases of surgical general anesthesia:
    * Premedication
    *Induction
    * Maintenance

Premedication

- **(pre-anethetic medication)**

- Relief from anxiety and produce amnesia: benzodiazepines

- Reduction of PS bradycardia & secretions;: Atropine-like drugs

- Prevention of postoperative emesis: metoclopramide

Induction

•patient goes from state of consciousness to a state of unconsciousness

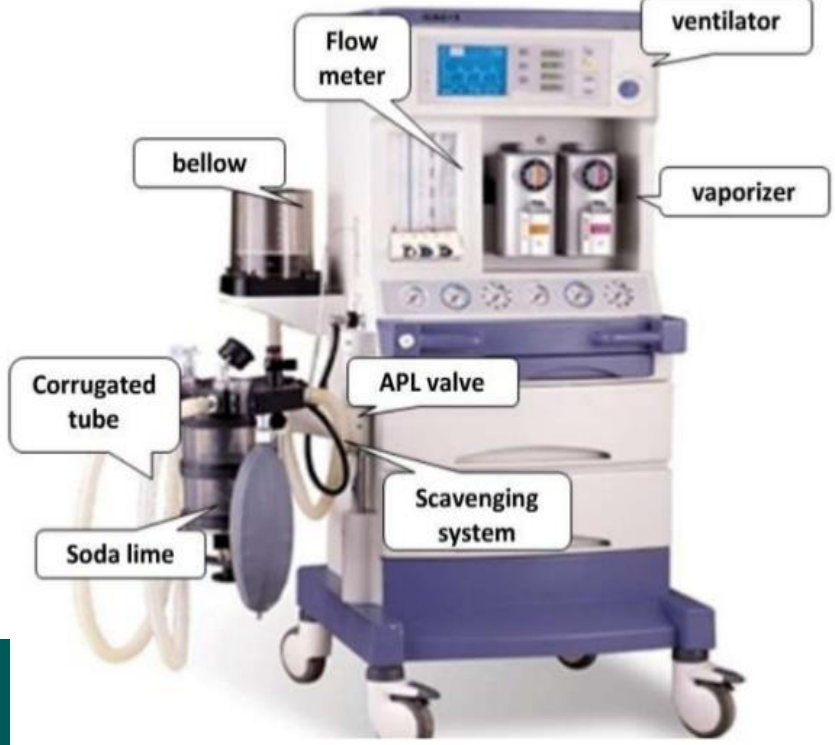
- **Intravenous propofol**, thiopental or etomidate produce a fast and smooth induction.

- **Neuromuscular blocking** agents decrease movement and provide muscle relaxation

•Maintenance

- Inhalation anesthetics are used to maintain a state of general anesthesia after induction (most cases).
- IV agents can be used via a continuous pump (Total intravenous anesthesia (TIVA)).

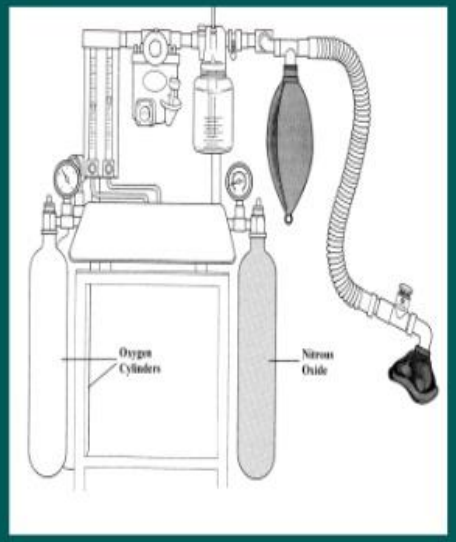
Anesthetic machine



Continuous flow (Boyle's) anaesthetic machine

Anaesthetic Machine (Boyle's equipment)

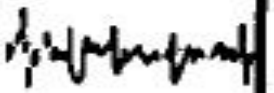
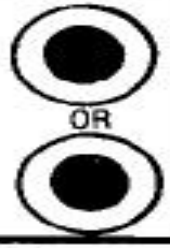
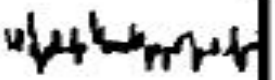
- The anaesthetic machine
- Gas source- either piped gas or supplied in cylinders
- Flow meter
- Vaporisers
- Delivery System or circuit



Four stages of anesthesia: (described in 1930s): modern anesthetics improved speed of onset, recovery and safety

- Stage I (analgesia): loss of sensation but patient is still alert and speaking.
- Stage II (Excitement): CNS excitation+ BP (irregular) + respiratory rate irrigular + release of subconscious emotions.
- Stage III (surgical anesthesia): regular respiration + relaxed skeletal muscles + progressive decrease in eye reflexes till eye movement stops and pupil is fixed
- Stage IV (Medullary paralysis): overdose **fatal depression of RC and VMC**

Stages of general anesthesia

STAGE	PUPIL		RESP.	PULSE	B.P.
	USUAL SIZE	REACTION TO LIGHT			
1 ST INDUCTION				IRREGULAR	NORMAL
2 ND EXCITEMENT	 OR			IRREGULAR & FAST	HIGH
3 RD OPERATIVE				STEADY SLOW	NORMAL
4 TH DANGER				WEAK & THREADY	LOW

PDs of general anesthetic agents

- They depress all excitable tissues including CNS neurons, cardiac muscle and smooth and striated muscle .
- Different parts of the CNS have different sensitivities to these agents, however, the reticular activating system (which is responsible for consciousness) is among the most sensitive
- The medullary centers are less sensitive to the general anesthetics than other parts of the CNS.

Mechanism of action

1.Earlier theories suggested interaction with lipid membrane bilayer:

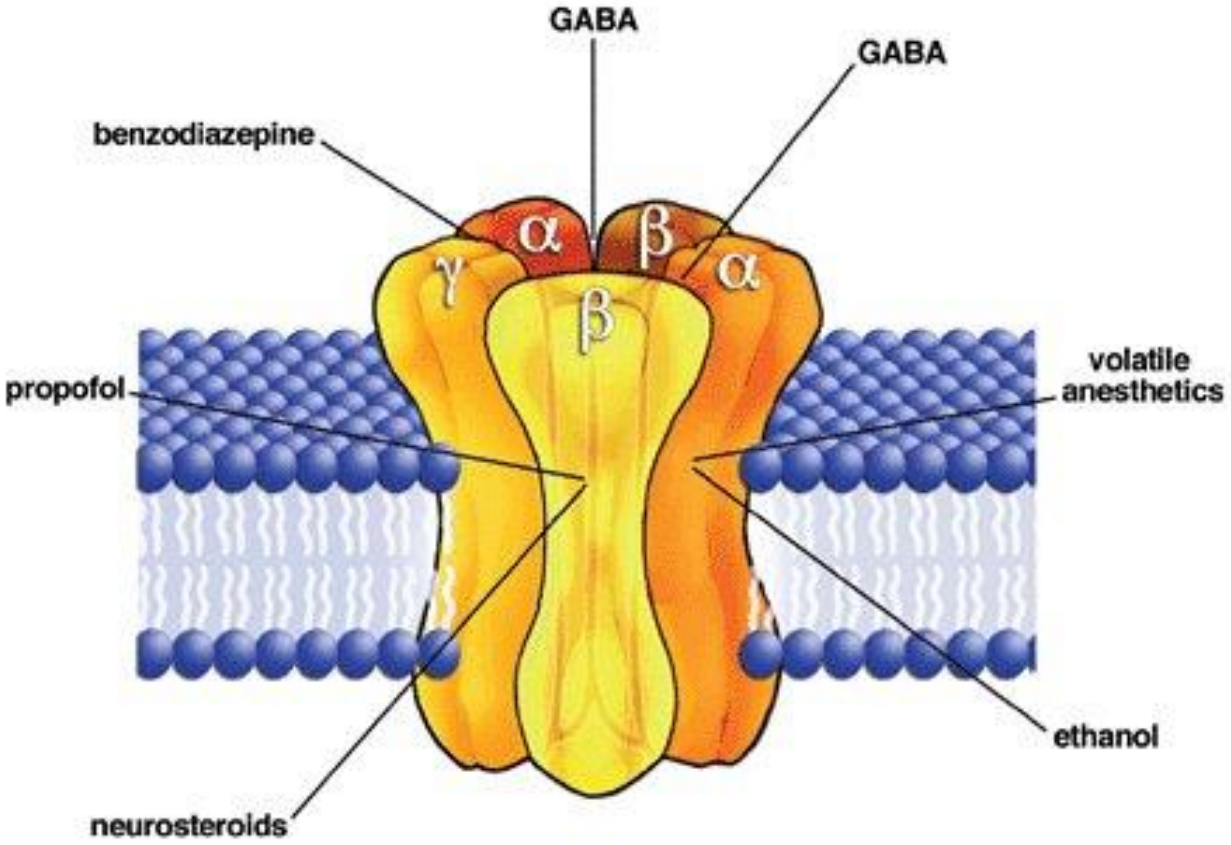
The **Meyer–Overton hypothesis** is the theory of anesthetic action which proposes that the potency of an anesthetic agent is related to its lipid solubility.

- Lipid-soluble anesthetic agent dissolves in brain tissues interrupting physical and chemical properties of neurons.

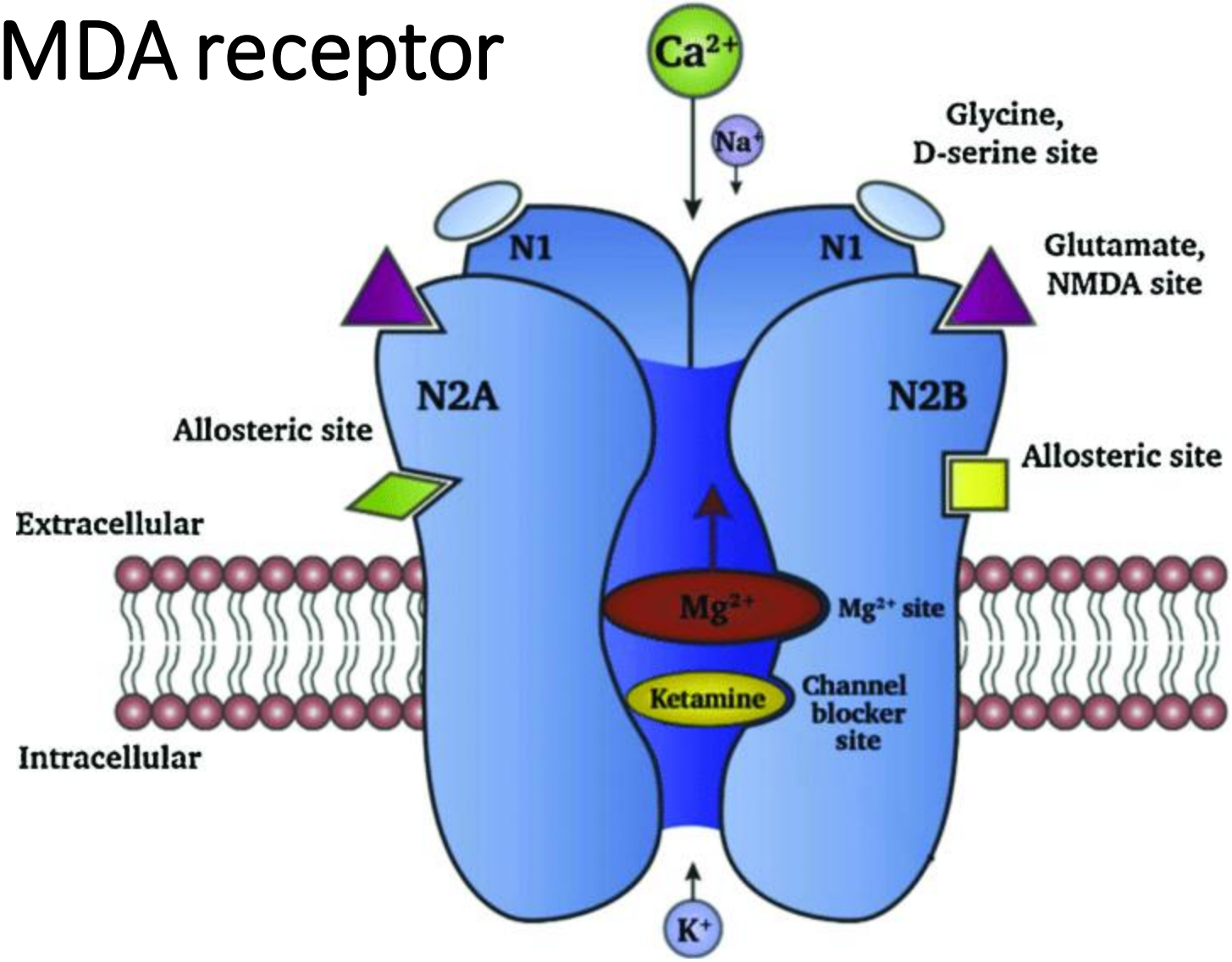
2- Modern theories:

- Activation of $GABA_A$
- Blocking of NMDA receptors
- Opening of two-pore K+ channels (K2P)

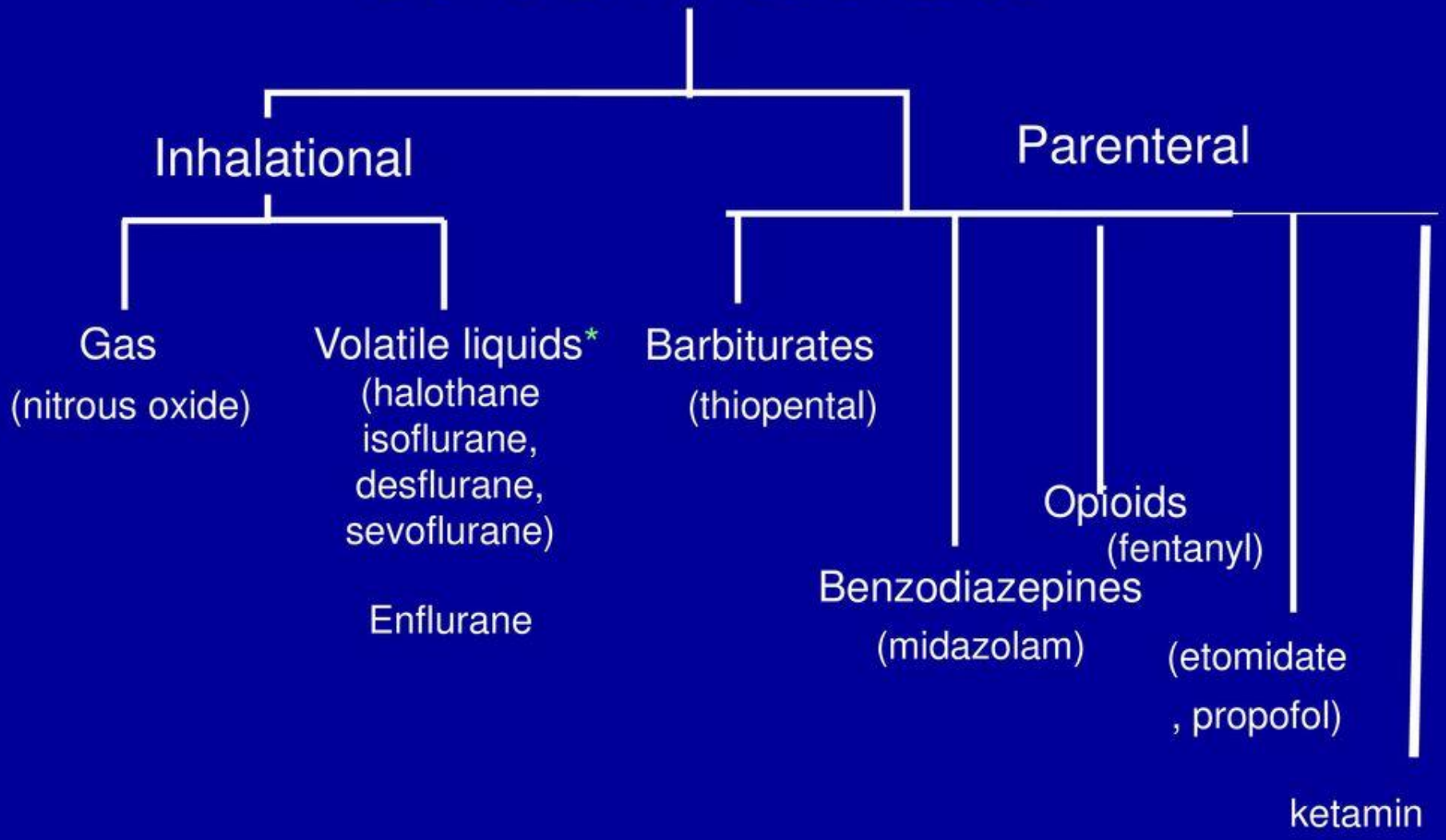
GABA A receptor



NMDA receptor



General Anesthetics



Inhalation Anesthesia

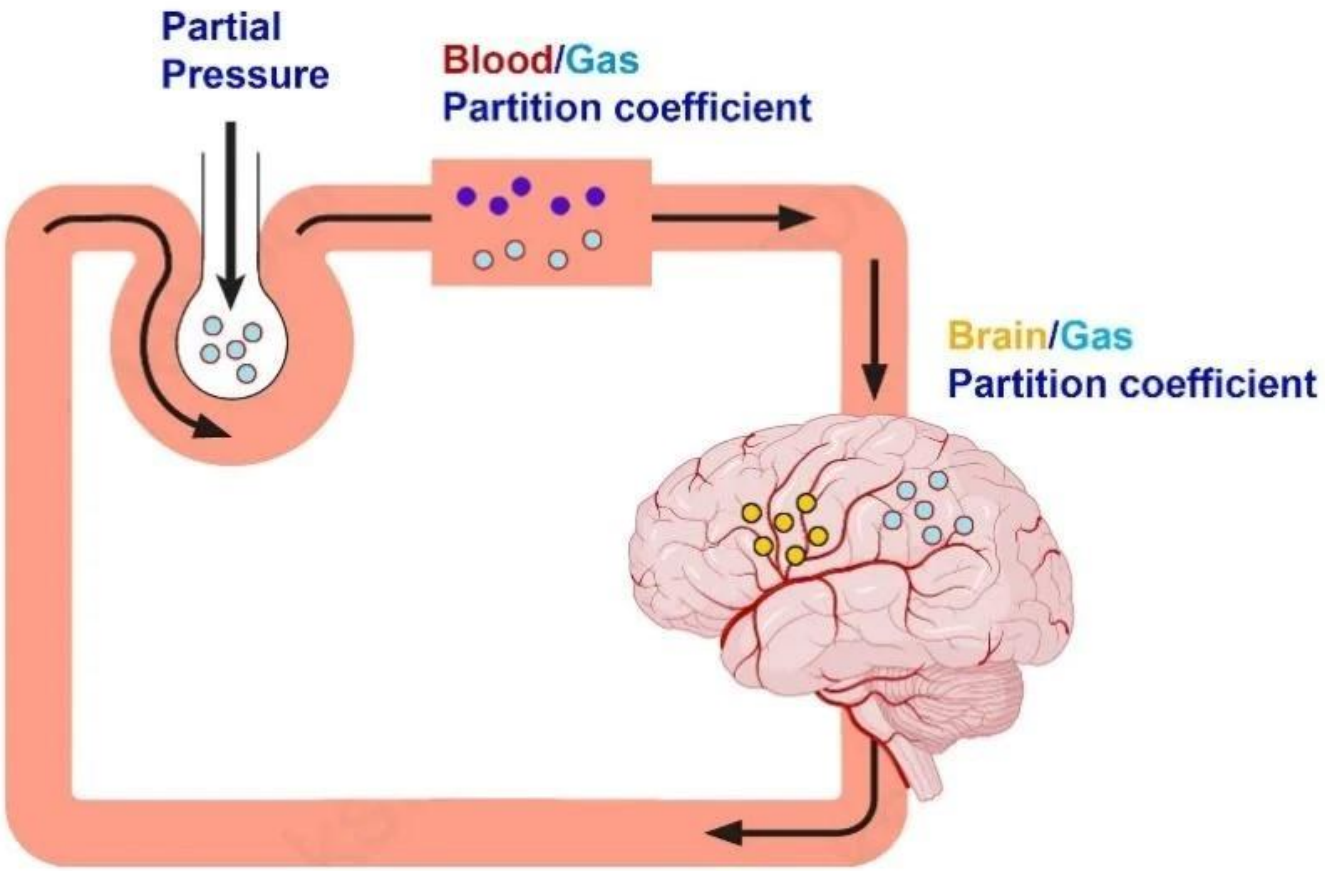
Drugs are introduced into the respiratory system by means of an anesthetic machine with the use of vaporizers.

Pharmacokinetics of Inhalation Agents

* Rapid induction and recovery are important properties of an anesthetic agent → allowing flexible control over the arterial tension (and hence brain tension) →depth of anesthesia

The depth of anesthesia →directly related to partial pressure of the agent in the blood, as this determine the conc. Of anesthetic in the CNS (proportionally-related to partial gas pressure in alveoli delivered by the machine.)

PKs of inhalational anesthesia



Blood/gas partition coefficient

- Agents of low blood solubility (e.g., nitrous oxide, desflurane) produce rapid induction and recovery

because free gas molecules more than bound gas form and so the arterial tension (and hence brain tension) rises and falls quickly

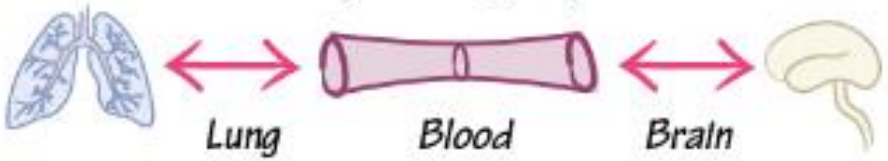
- Brain/gas partition coefficient: high

- Agents of high blood solubility (e.g., halothane)

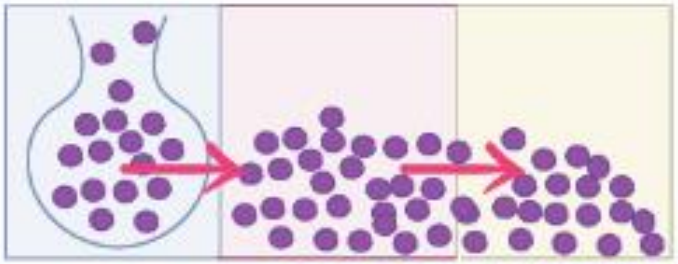
because free gas molecules are less than bound gas form, so they have much slower induction and recovery times

- Brain/gas partition coefficient: low

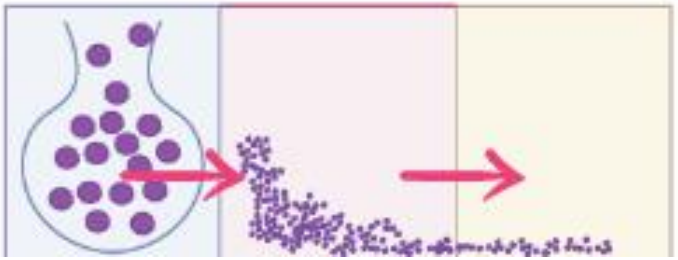
Blood/Gas Partition Coefficient: λ(blood/gas)



POORLY SOLUBLE
↓ λ(blood/gas)



HIGHLY SOLUBLE
↑ λ(blood/gas)



Adverse effects of inhaled anesthetics

1- Malignant Hyperthermia

- Malignant hyperthermia (MH) is a pharmacogenetic hypermetabolic state of skeletal muscle
- Induced *in susceptible individuals* by inhalational anesthetics and/or succinylcholine.

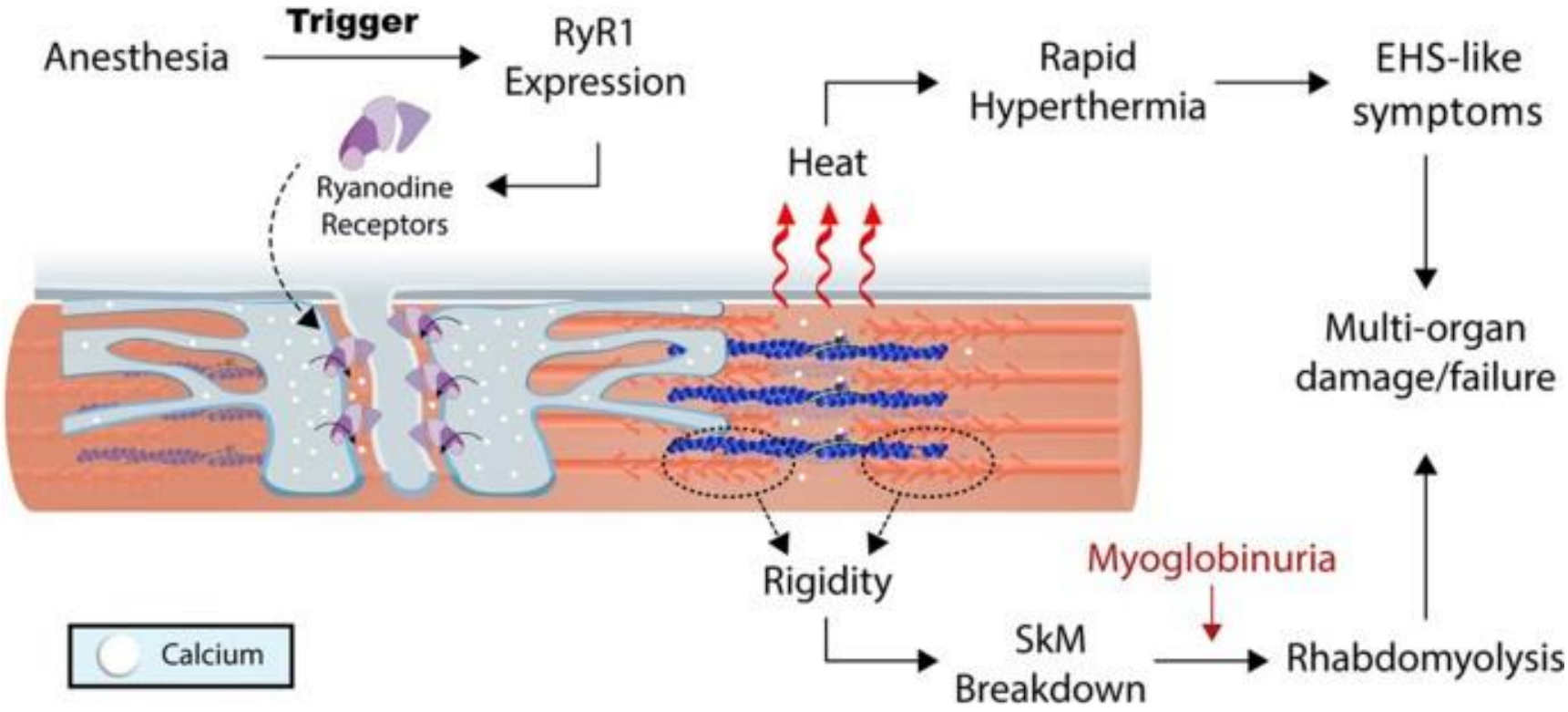
Malignant Hyperthermia

- Genetic Ca^{+} channel defect or RYR1 (ryanodine receptor)
- Excess calcium ion release from SR leads to excessive ATP breakdown/depletion
- **Signs**: tachycardia, tachypnea, metabolic acidosis, hyperthermia, muscle rigidity, sweating, arrhythmia

- May be fatal: 75% mortality

- Treated with dantrolene IV: close Ca channels: life-saving.

Malignant hyperthermia



- 2- CNS: increased ICT due to VD
- 3- CVS: **Most agents, particularly halothane, depress** myocardial contractility and produce **bradycardia**.
- This decreases cardiac output and blood pressure (except??)
- ***Halothane also sensitizes the heart to catecholamines, which*** can lead to arrhythmias

- 4- Respiratory:
- Bronchodilatation except desflurane: laryngospasm and bronchoconstriction.
- 5- Liver:

•Most agents decrease liver blood flow.

• Mild hepatic dysfunction

•Halothane:

•About 1 in 30000 people will develop severe hepatic necrosis following the use of ***halothane, especially after repeated exposure*** within 3-months.

•This is because of interaction of reactive metabolites with cellular proteins, which initiate an autoimmune reaction.

•Hepatotoxicity has resulted in the decreased use of ***halothane, and avoidance of repeat use*** within 3 months

•6- Uterus:

•**There is relaxation of the uterus, which may increase the risk of** hemorrhage if anesthesia is used in labor.

•Nitrous oxide has less effect on uterine muscle compared with the other agents

IV anesthetic drugs

- **Include:**
- **propofol, thiopental, etomidate, ketamine, midazolam**
- **Indications:**

-short surgical procedures: diagnostic endoscopy, cardiac catheterization, abscess removal, episiotomy, etc. …

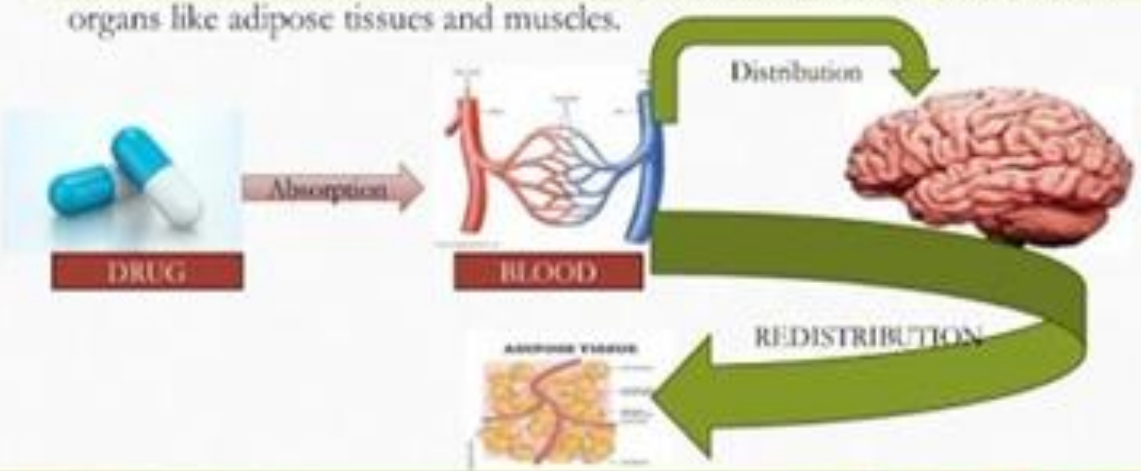
- Longer procedures: TIVA

- Rapid induction followed by an inhalational agent

- They are highly lipid-soluble agents and cross the BBB rapidly; (onset <30 seconds), duration of action (minutes) (Redistribution).

What is redistribution of drugs ?

- Movement of drugs from specific tissues to plasma and then less perfused organs like adipose tissues and muscles.



Thiopental	Ketamine	Propofol (diprivan)
Pharmacological properties		
1. IV barbiturate. 2. Short duration of anesthesia (about 2-5 min).: ultra-short 3. Only for Rapid induction but slow recovery (sedation up to 24 hs)??	1. It produces **dissociative anaesthesia** (i.e. patient appears awake (nystagmic gaze) and hallucinates but unconscious and doesn't feel pain. **2. Good analgesia.** 3. Associated with a **bronchodilator effect due** to ↑ sympathetic outflow. 4. No depression of respiration 5. More tolerable in children 6. Blocker of NMDA receptors	1. Rapid induction & recovery. 2. Postoperative nausea and vomiting are less than with other agents. Propofol has an anti-emetic action. 3- the most used
Disadvantages		
1. ↓↓ BP & bradycardia 2. Thiopental solution is alkaline, it must be strictly given IV: leakage leads to tissue necrosis and gangrene	1. ↑ **sympathetic outflow** →cardiac stimulation & ↑BP. (contraindicated in hypertensives or those with stroke) 2**. ↑ cerebral blood flow →** post-operative hallucinations & nightmares.	· 1- causes pain at injection site • 2- propofol-infusion syndrome: acidosis, rhabdomyolysis, kperkalemia, renal failure, lipemia, arrhythmia, circulatory collapse • Fospropofol: better

- **Etomidate:**
- **Advantages:**
- 1- less CVS depression 2- no RC depression
- 3- no tissue necrosis if leaked
- **Disadvantages:**
- 1- acute adrenal suppression if given in presence of sepsis with high mortality rate
- 2- post-operative nausea and vomiting
- **Midazolam**:
- short-acting benzodiazepine (5-10 min.) due to drug redistribution
- Used for short surgical procedures
- Antidote: flumazenil

Thank you