Pharmacology of General Anesthetics

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Objectives

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. Describe the main pharmacokinetic and pharmacodynamic characteristics of the intravenous anesthetics

General Anesthesia

General anesthesia is a Reversible State of CONTROLLED unconsciousness produced by anesthetic agents and characterized by loss of the body sensations, analgesia, 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 with safe therapeutic window, so:

Balanced Anesthesia

•A combination of agents (balanced anesthesia) is used in the **clinical phases of surgical general anesthesia:**

- ❑ Premedication
- ❑ Induction
- ❑ Maintenance
- ❑ Recovery

Premedication (preanesthetic drugs)

- Relief from anxiety and produce amnesia: opioids, benzodiazepines, barbiturates

- Reduction of PS stimulation: bradycardia & secretions: anticholinergics, antihistaminic drugs

- Prevention of postoperative emesis: anticholinergics, antihistaminics and metoclopramide

- Muscle relaxants

Induction

•**Patient goes from the state of consciousness to a state of unconsciousness: transition phase from awake to full anesthetic effect on CNS.**

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

- **Inhalation method**: **for special patients**: **difficult air ways** and **children** (mask or hand introduced gradually from the side)

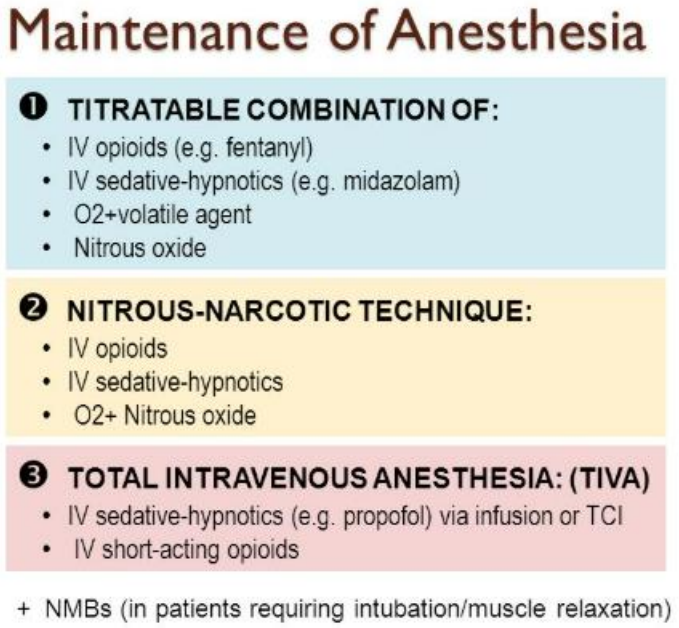
Maintenance

- **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)**)

- Monitoring of:

- HR
- BP
- Pupil size, lacrimation
- Movement

- NB: TCI: target controlled infusion

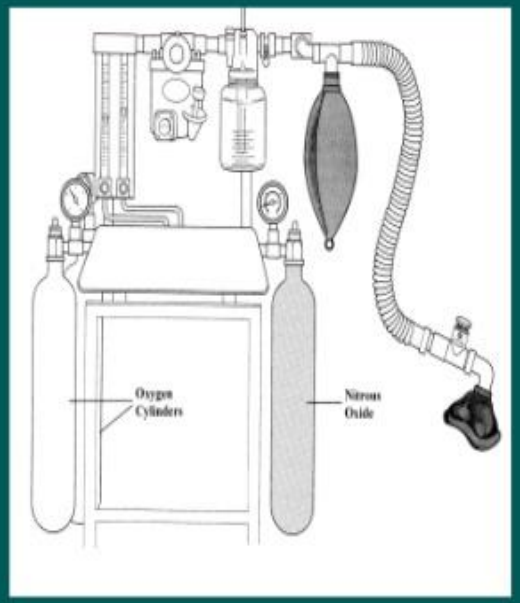


Anesthetic Machine

Continuous flow (Boyle's) anaesthetic machine

Anaesthetic Machine (Boyle's equipment)

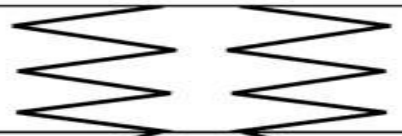
- The anaesthetic machine
- Gas source- either piped gas or supplied in cylinders
- Flow meter
- Vaporisers
- Delivery System or circuit



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 irregular, 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 Anesthesia

Stage	Muscle tone	Breathing	Eye movement
1 Analgesia	Normal		Slight
2 Excitement	Normal to markedly increased		Moderate
3 Surgical anaesthesia	Slightly relaxed		Slight
	Moderately relaxed		None
	Markedly relaxed		None
	Markedly relaxed		None
4 Respiratory paralysis	Flaccid		None

Pharmacodynamics Of General Anesthetic Agents

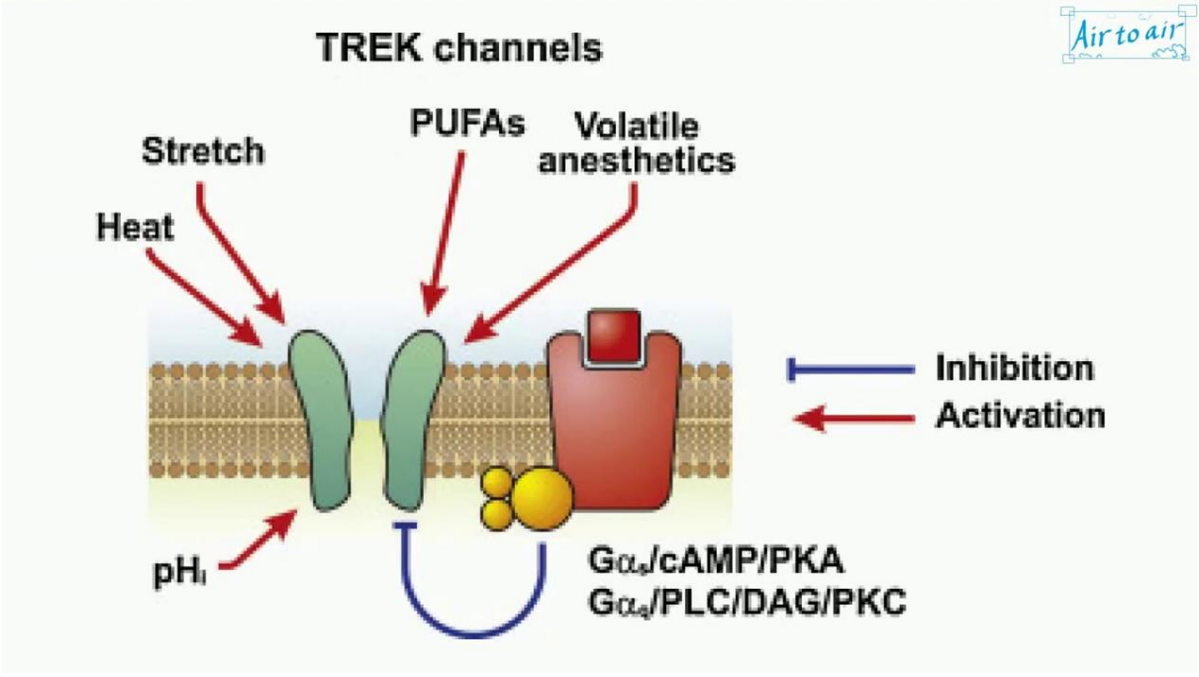
- Anesthetic agents absorbed to blood stream then **pass BBB**
- Enters **specific cells in CNS**, where they act on **specific receptors**
- There effects are **reversible**
- They **depress all excitable tissues** including CNS neurons, cardiac muscle and smooth and skeletal muscle fibers .
- Different 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 least sensitive**

PDs of anesthetic agents

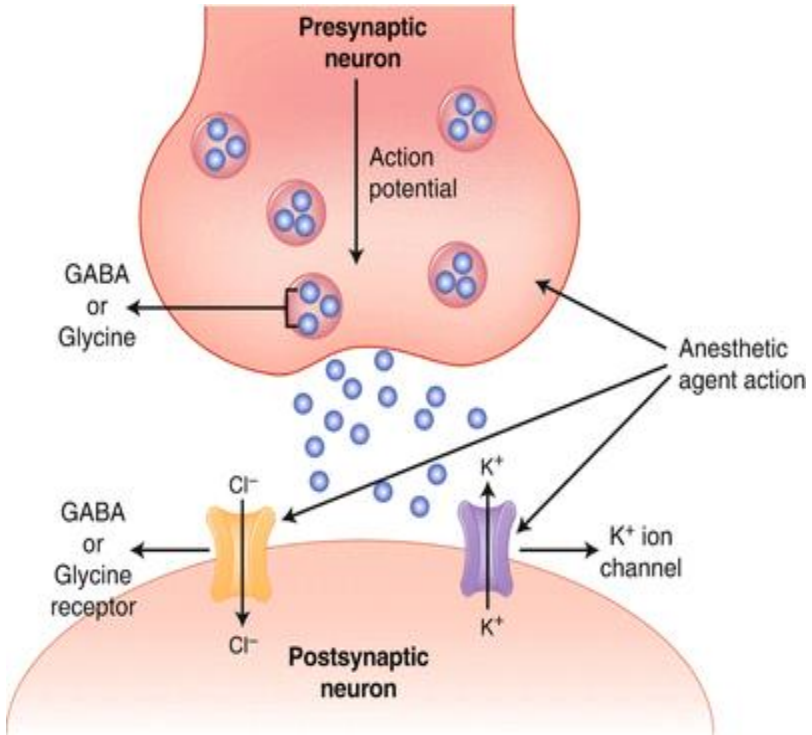
- **General anesthetics depress the following CNS parts:**
- **Reticular activating system**: reversible loss of consciousness
- **Prefrontal cortex, hippocampus and amygdala:** amnesia
- **Spinal cord**: immobility and analgesia

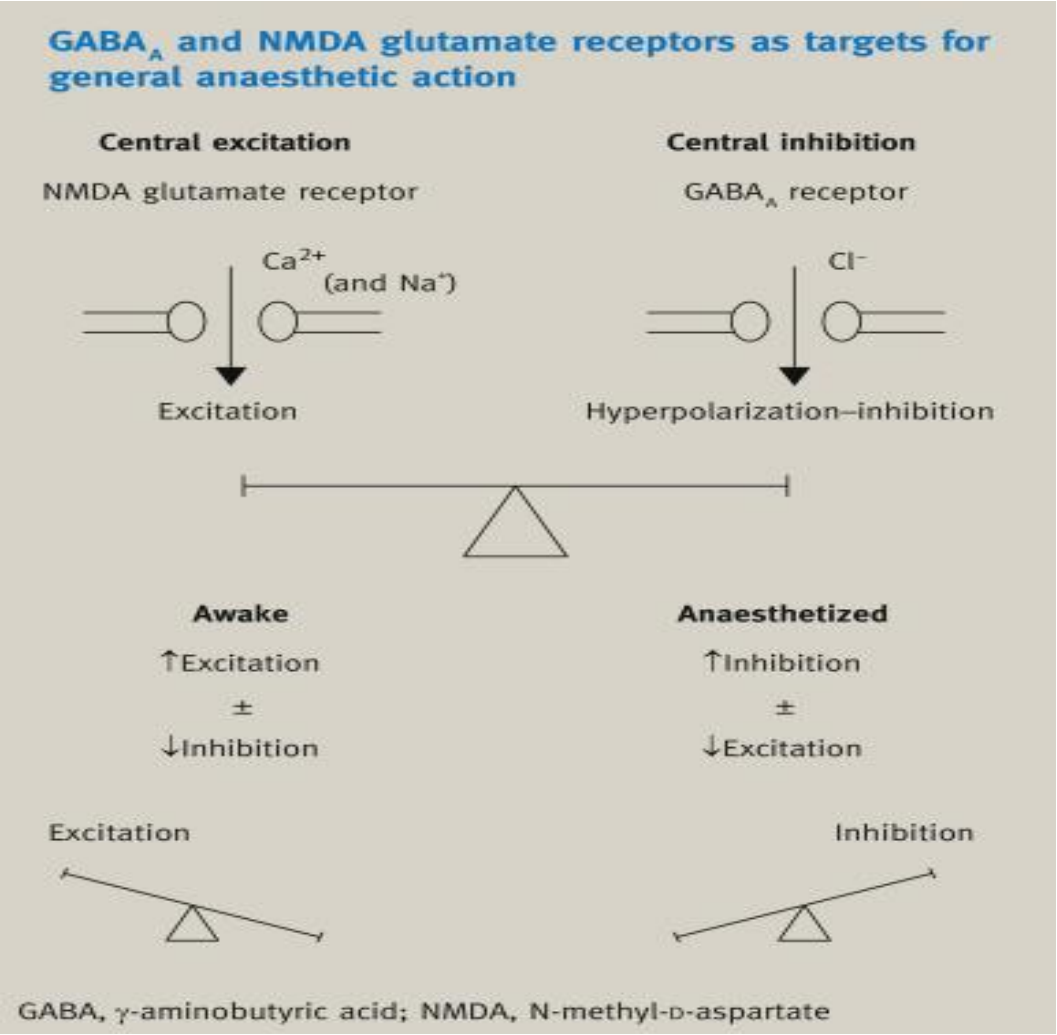
Mechanism Of Action

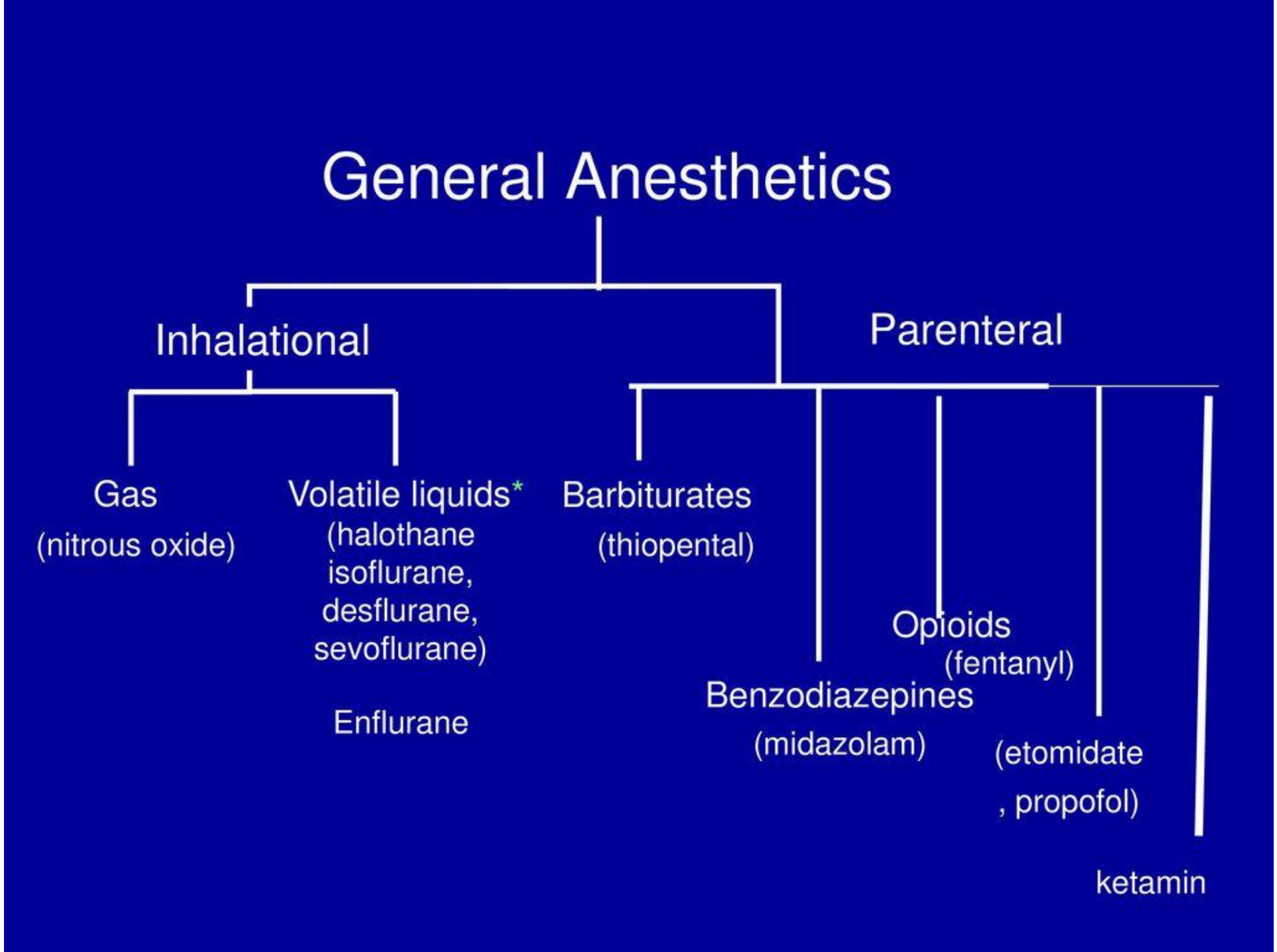
- 1- **Activation of $GABA_A$**
- 2- **Blocking of NMDA receptors**
- 3- **Opening of two-pore K+ channels (K2P):** Two-pore domain potassium (K2P) channels are responsible for leak K+ currents that stabilize the resting membrane potential and regulate neuronal excitability



Mechanism Of Action Of General Anesthesia






General Anesthetics
Inhalational
Parenteral
Gas
(nitrous oxide)
Volatile liquids*
(halothane
isoflurane,
desflurane,
sevoflurane)
Enflurane
Barbiturates
(thiopental)
Benzodiazepines
(midazolam)
Opioids
(fentanyl)
(etomidate
, propofol)
ketamin

Inhalation Anesthesia

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

Pharmacokinetics of Inhalation Agents

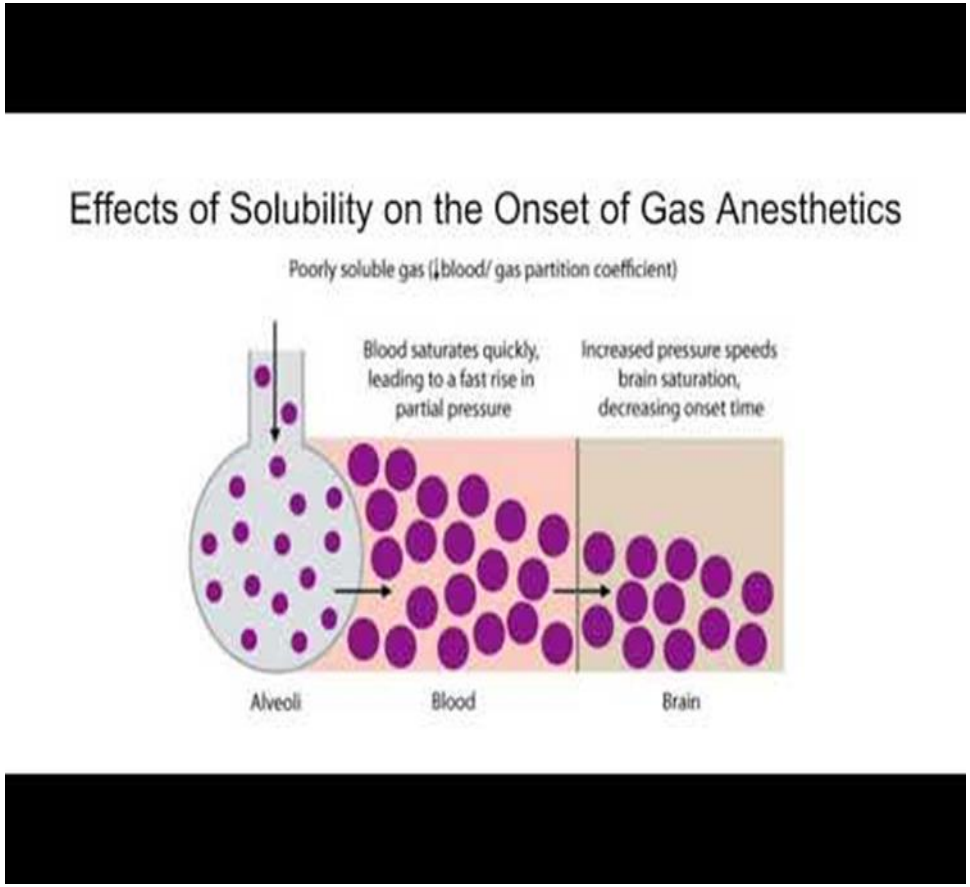
- **Factors affecting both flexible control and depth of anesthesia:**
- **1- Partial pressure in alveoli**
- **2- Arterial tension (partial pressure or concentration) of anesthetic agent**
- **3- Brain tension**
- **4- Rate of induction and recovery**
- **All of these factors are affected by:**
- **Blood/Gas Partition Coefficient: (λb/g)**

Blood/Gas Partition Coefficient

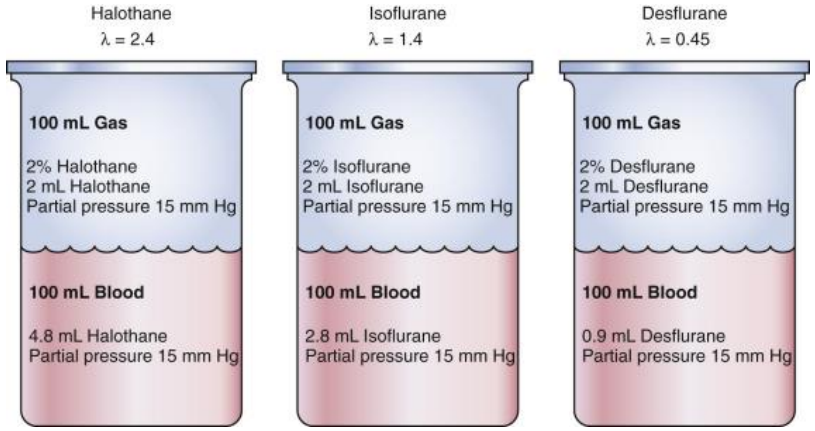
- **Agents of low blood solubility**
- (e.g., nitrous oxide, desflurane): **rapid induction and recovery**
- because free gas molecules more than bound gas form and so the arterial tension (and hence brain tension) **rises and falls quickly**
- **Brain/gas partition coefficient: high**

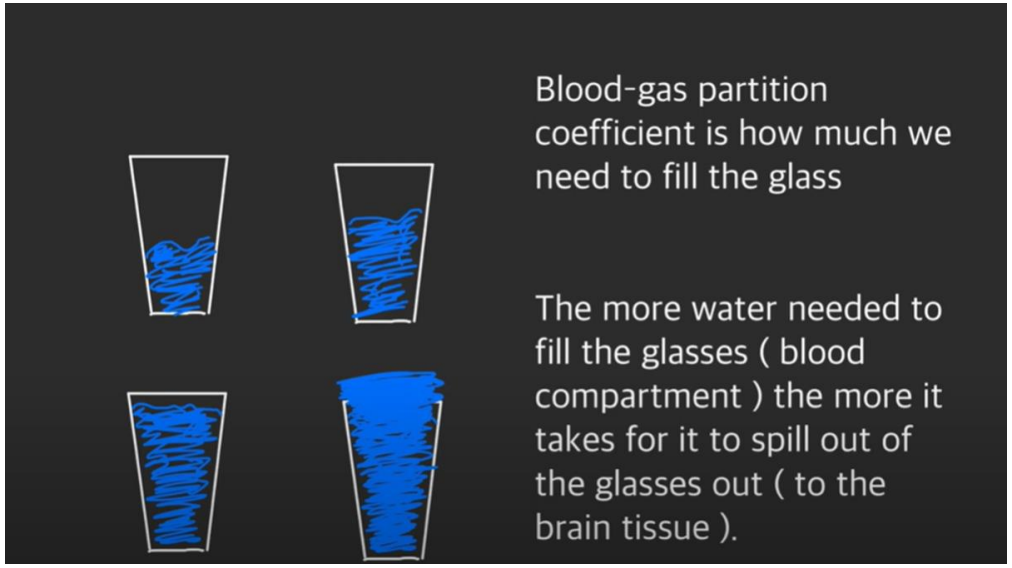
- **Agents of high blood solubility**
- (e.g., halothane): **slow induction and recovery**
- because free gas molecules are less than bound gas form, so the arterial tension (and hence brain tension) **rises and falls slowly**

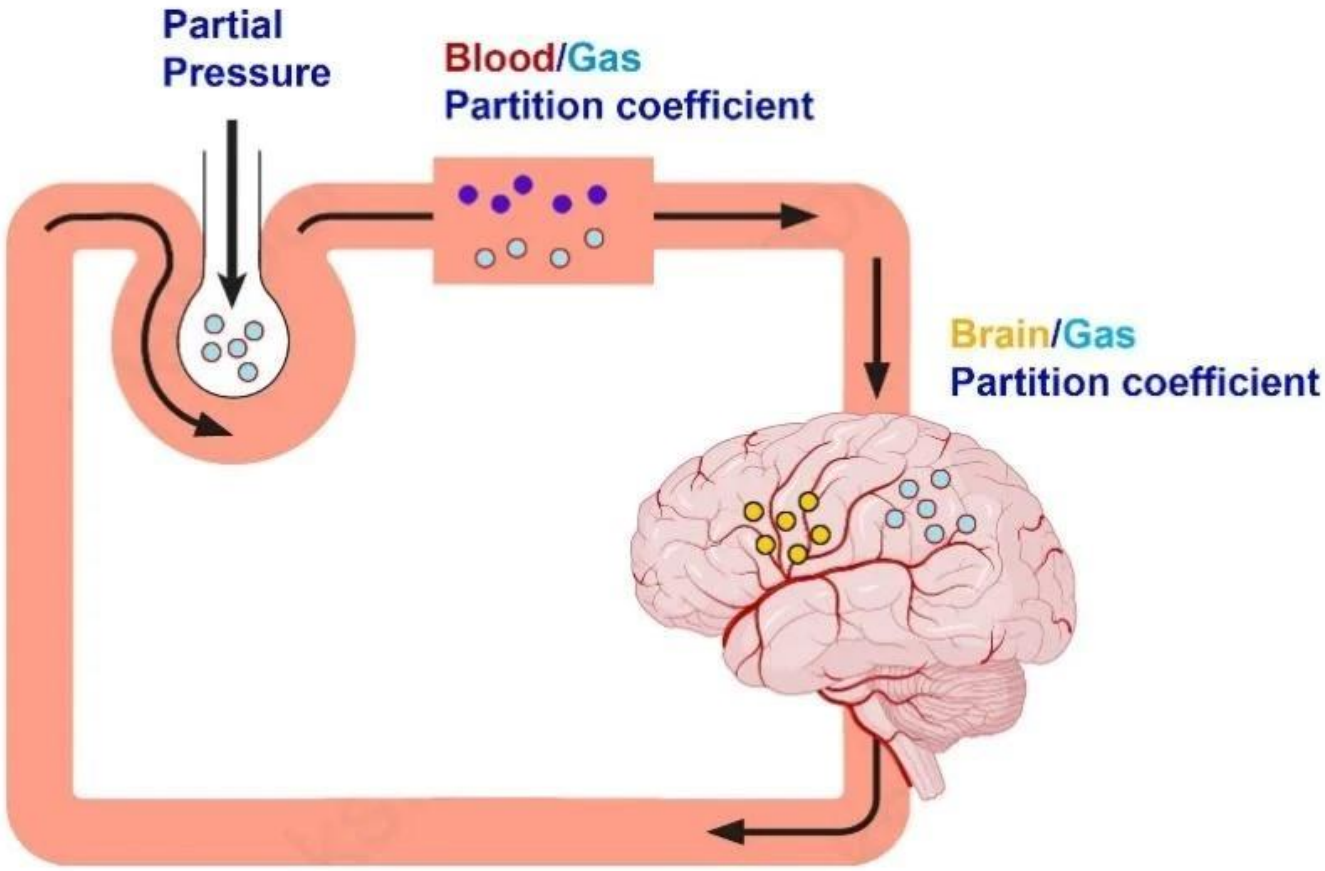
- **Brain/gas partition coefficient: low**



PKs of inhalational anesthesia





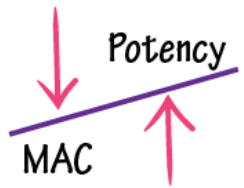


General Principles

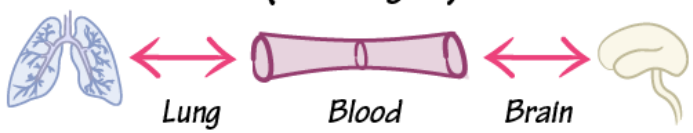
Lipophilicity

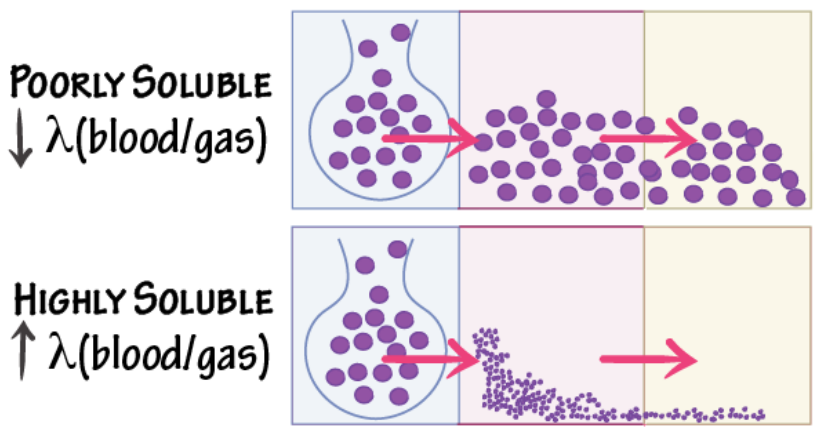
↑ Lipophilicity → ↑ Ability to cross neuronal membranes → ↑ Potency

Mean Alveolar Concentration (MAC)



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





Properties of Inhaled Anaesthetics

Minimal Alveolar Concentration (MAC)

- Smaller the MAC value more potent is the anaesthetic and vice versa.

Arteriovenous concentration Gradient(ACG)

- Smaller the ACG value faster will be the onset of action and vice versa.

Blood – Gas partition coefficient

- Smaller the B/G partition coefficient value faster will be the onset of action and vice versa.

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

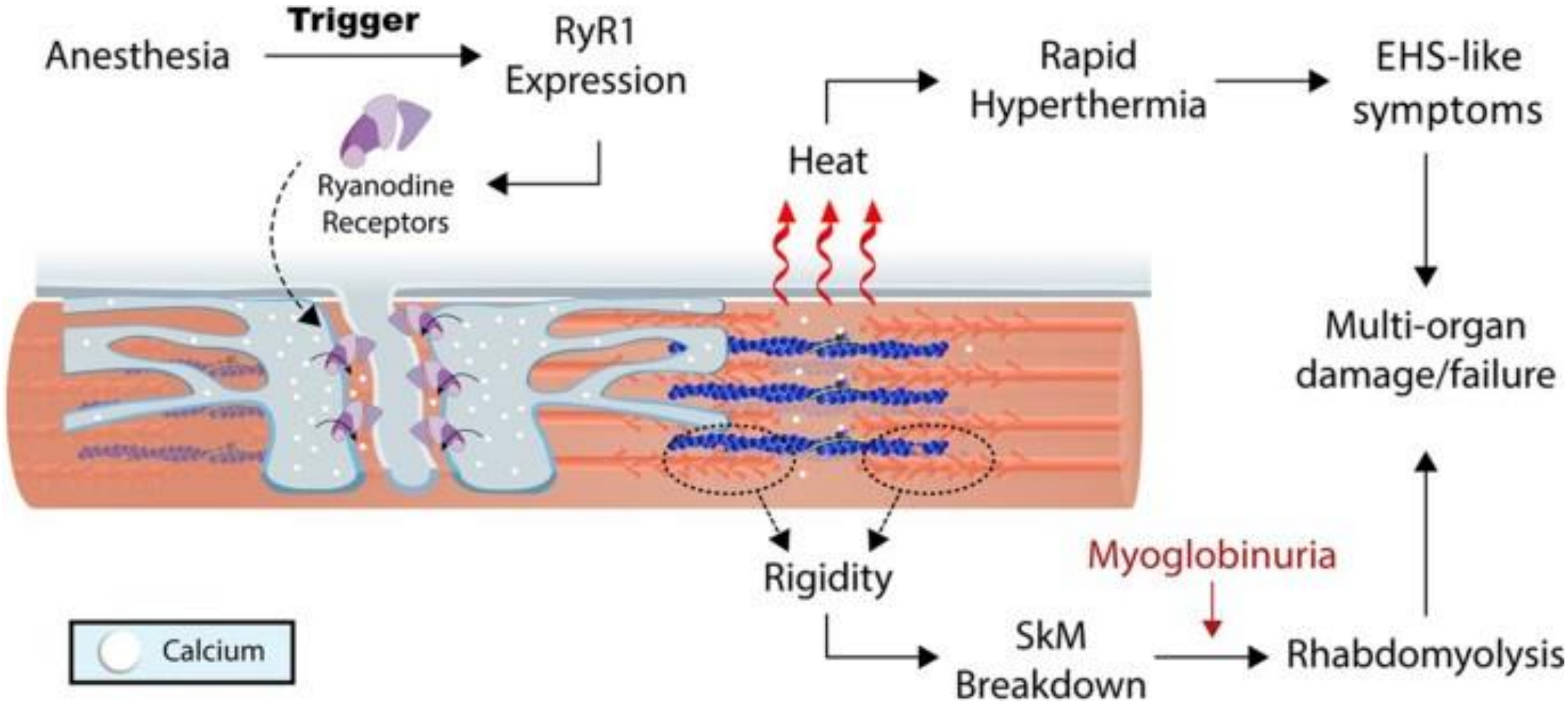
- Genetic Ca^{+} channel defect or RYR1 (ryanodine receptor)

- Excess calcium ion release from SR leads to excessive ATP breakdown/depletion

- **Signs**: tachycardia, arrhythmia, tachypnea, metabolic acidosis, hyperthermia, muscle rigidity, sweating

- **May be fatal**: 75% mortality

- **Treatment**: dantrolene IV: close Ca channels: LIFE-SAVING.


Anesthesia
Trigger
RyR1
Expression
Ryanodine
Receptors
Heat
Rapid
Hyperthermia
EHS-like
symptoms
Multi-organ
damage/failure
Rigidity
Myoglobinuria
SkM
Breakdown
Rhabdomyolysis
Calcium

Adverse effects of inhaled anesthetics

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

•4- Respiratory:

•Broncho-dilatation 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:**
- **ketamine, etomidate, fentanyl, propofol, thiopental, midazolam**
- **Indications:**

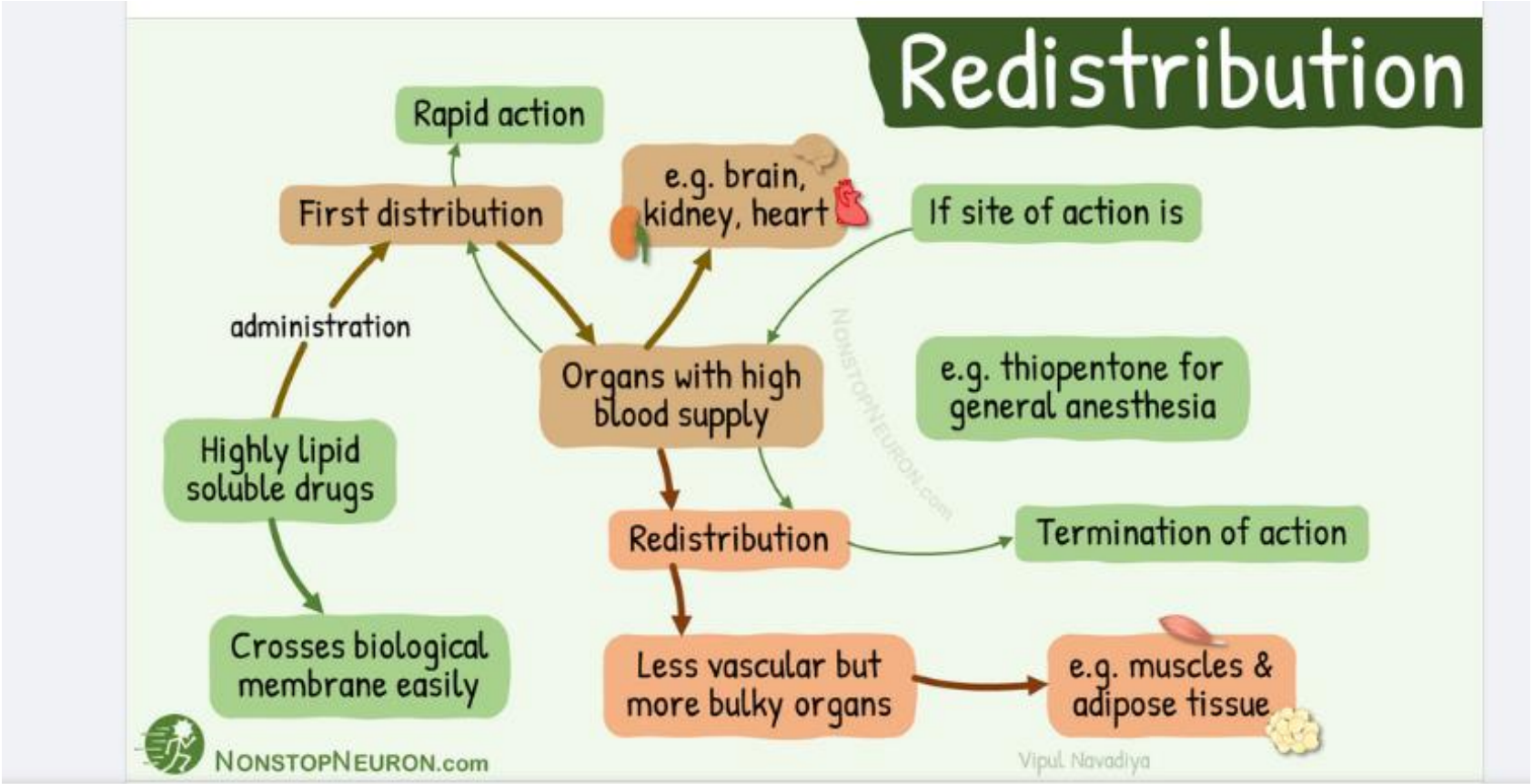
1-Short surgical procedures: diagnostic endoscopy, cardiac catheterization, abscess removal, episiotomy, etc. …

2- Longer procedures: TIVA

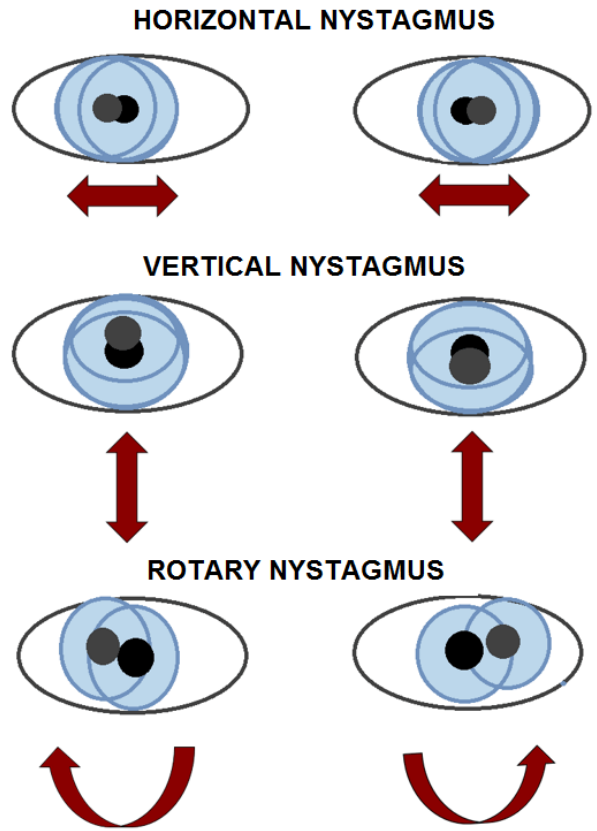
3- Rapid induction followed by an inhalational agent

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

Redistribution



Thiopental	Ketamine	Propofol (diprivan)
Pharmacological properties		
1. **IV** barbiturate. 2. **Ultra-Short duration** of anesthesia (about 2-5 min) 3. Only for **Rapid induction but slow recovery** (**sedation up to 24 hrs.)**	1. It produces **dissociative anesthesia** (i.e. patient appears **awake** (**nystagmus gaze**) and **hallucinates** but **unconscious** with **analgesia** **2. Good analgesia.** 3. Associated with a **STRONG 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- Anticonvulsant** **4- Bronchodilator** **3- The most used** **4- Enhances GABA receptors** **7- Urine: neon green**
Disadvantages		
1. ↓↓ BP & bradycardia **2. Respiratory depression** 3. 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 hypertensive pateints or those with stroke)** 2. ↑ **Cerebral blood flow** → **post-operative hallucinations & nightmares.** **3. Increased salivation**	1- **Pain at injection site** **2- Propofol-infusion syndrome**: rhabdomyolysis, acidosis, lipemia, kperkalemia, renal failure, arrhythmia, circulatory collapse ▪ **Fospropofol**: better


HORIZONTAL NYSTAGMUS
VERTICAL NYSTAGMUS
ROTARY NYSTAGMUS

- **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**: enhances GABA receptors
- **Duration: (5-10 min.)** due to drug **redistribution**
- **Advantages: Decreases cerebral blood flow- anticonvulsant**
- **Disadvantages: Mild hypotension- respiratory depression**
- Used for short surgical procedures
- **Antidote**: **flumazenil**

Thank you