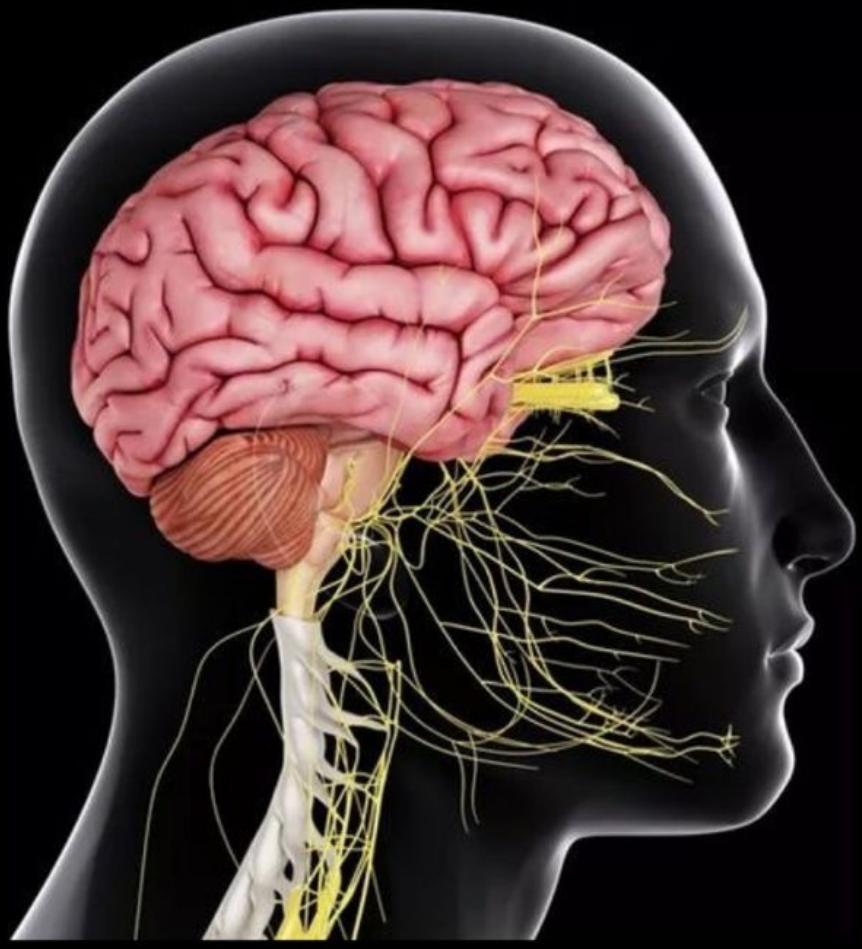
# CENTRAL NERVOUS SYSTEM



SUBJECT : Pharmacology

LEC NO. : 8

DONE BY : Batool ALzubaidi

وَقُل رَّبِّ زِدْنِي عِلْمًا

# Anesthetics

To facilitate surgery

Pharmacology and Toxicology

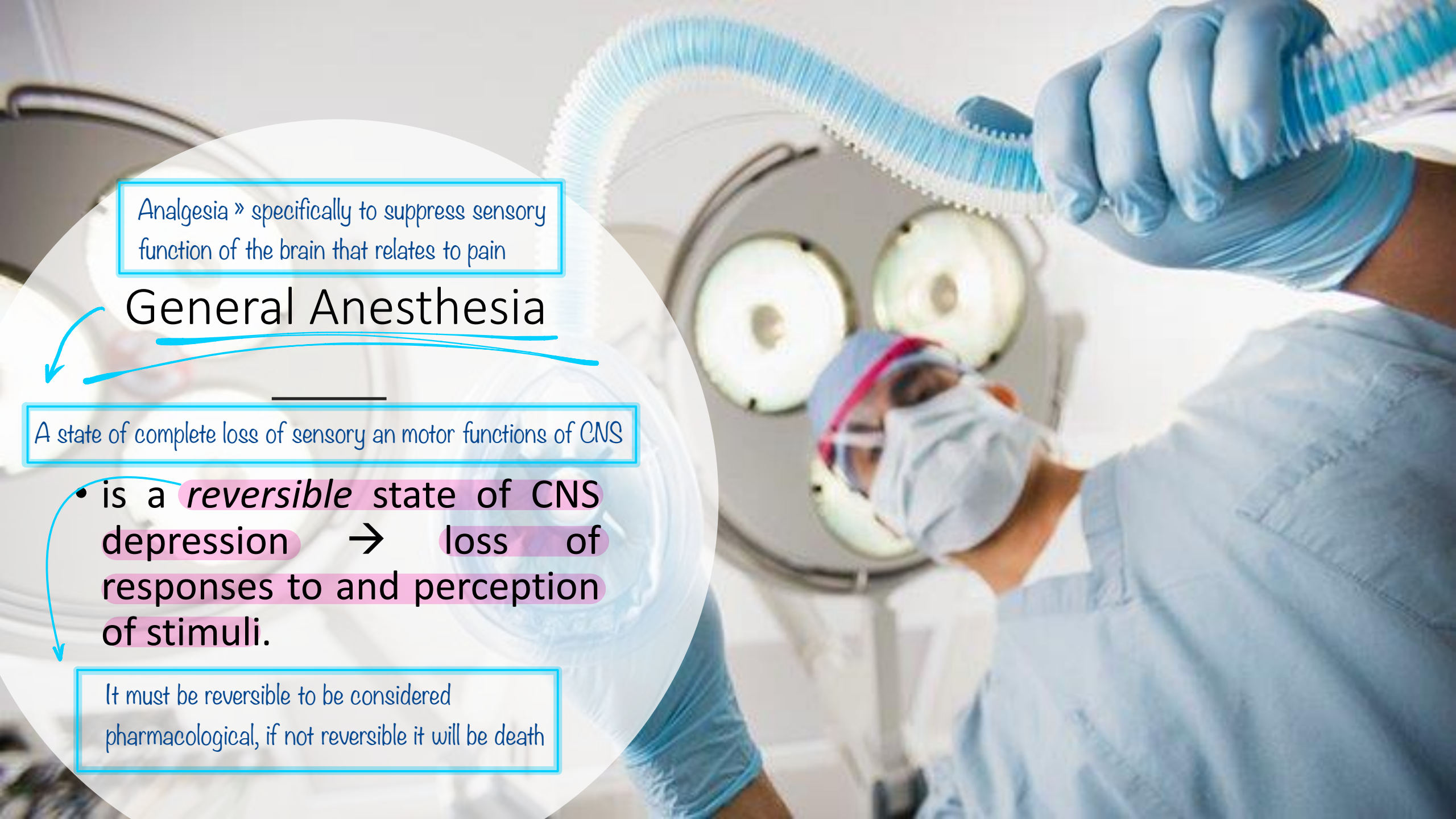
Central Nervous System Module

Third Year Medical Students

Tareq Saleh

Faculty of Medicine

The Hashemite University



Analgesia » specifically to suppress sensory function of the brain that relates to pain

# General Anesthesia

A state of complete loss of sensory an motor functions of CNS

- is a *reversible* state of CNS depression → loss of responses to and perception of stimuli.

It must be reversible to be considered pharmacological, if not reversible it will be death

# Why are they "general"?

- **Sensory**
  - -Absence of intraoperative pain

Loose ability to sense pain, memory » analgesic part of anesthesia

- **Cognitive**:
  - -Absence of intraoperative awareness
  - -Absence of recall of intraoperative events
- **Motor**:
  - -Absence of movement
  - -Adequate muscular relaxation

Complete loss of movement » to facilitate smoothness of surgery, patient must stay still to avoid injuries .. muscular relaxation isn't selective respiratory muscles will also be affected » you can't perform a successful anesthesia without mechanical ventilator support

- **Autonomic**:
  - -Absence of hemodynamic response
  - -Absence of tearing, flushing, sweating, and gastric secretions

You must monitor blood pressure

# What are the benefits of anesthesia?

- Sedation and reduction of anxiety
- Lack of awareness and amnesia
- Analgesia
- Skeletal muscle relaxation
- Suppression of undesirable reflexes

# What is the “perfect” anesthetic?

- chemical stable with low flammability
- produces “reversible” loss of consciousness

If not it will cause death

- produces analgesia, suppresses reflexes and produces muscle relaxation

Best anesthetic » what doesn't cause cardiovascular depression

- minimal cardiovascular and respiratory side effects

Main complication of analgesia

- cheap and easy to manufacture and administer

Elderly with comorbidity are at higher risk

NO SINGLE DRUG HAS ALL THESE CHARACTERISTICS!

Solution » to use a combination of drugs that can induce anesthesia, maintain anesthesia, facilitate intubation, induce memory loss, analgesics

# Solution

Several categories of drugs are combined!

**PREANESTHETIC MEDICATIONS**

Antacids
Anticholinergics
Antiemetics
Antihistamines
Benzodiazepines
Opioids

**NEUROMUSCULAR BLOCKERS (see Chapter 5)**

*Cisatracurium, pancuronium, rocuronium, succinylcholine, vecuronium*

**GENERAL ANESTHETICS: INTRAVENOUS**

Barbiturates
Benzodiazepines
*Dexmedetomidine* PRECEDEX
*Etomidate* AMIDATE
*Ketamine* KETALAR
Opioids
*Propofol* DIPRIVAN

**GENERAL ANESTHETICS: INHALED**

***Desflurane*** SUPRANE
*Halothane* FLUOTHANE
***Isoflurane*** FORANE
*Nitrous oxide* NITROUS OXIDE
***Sevoflurane*** ULTANE

# How do we choose the best combination?

# Patient Factors in The Selection of Anesthesia

## Cardiovascular

- Anesthetics suppress cardiovascular function
- Hypotension→↓ perfusion→ ischemia
- Patient's history is important

## Respiratory

- Inhalational/intravenous anesthetics and opioids depress respiration.
- Asthma/ventilation/anatomical abnormalities

## Hepatic/Renal

- Metabolism
- Clearance
- Drug-interaction, e.g., alcohol use

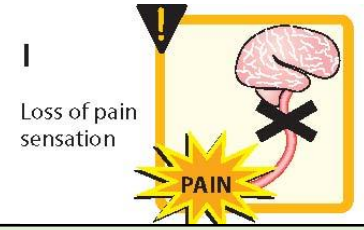
## Nervous

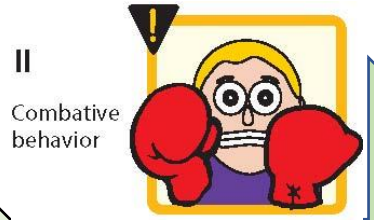
- Pre-existing neurological disorders e.g., epilepsy, myasthenia gavis

## Gestational

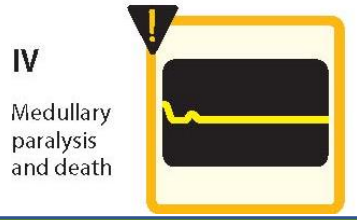
- Fetal organogenesis
- Postnatal complications

# Depth of Anesthesia








## STAGE I (Analgesia)

## STAGE II (Delirium)

## STAGE III (Surgical Anesthesia)

## STAGE IV (Medullary Paralysis)

**Partial analgesia** → **Drowsiness** → **Amnesia** → **Full analgesia** → **Irregularities in BP** → **Atonia/areflexia** **Severe depression of respiration**

Shortened or eliminated by giving IV anesthetics

Ideal stage for surgery

Death happens without ventilation/circulatory support

# Anesthetics

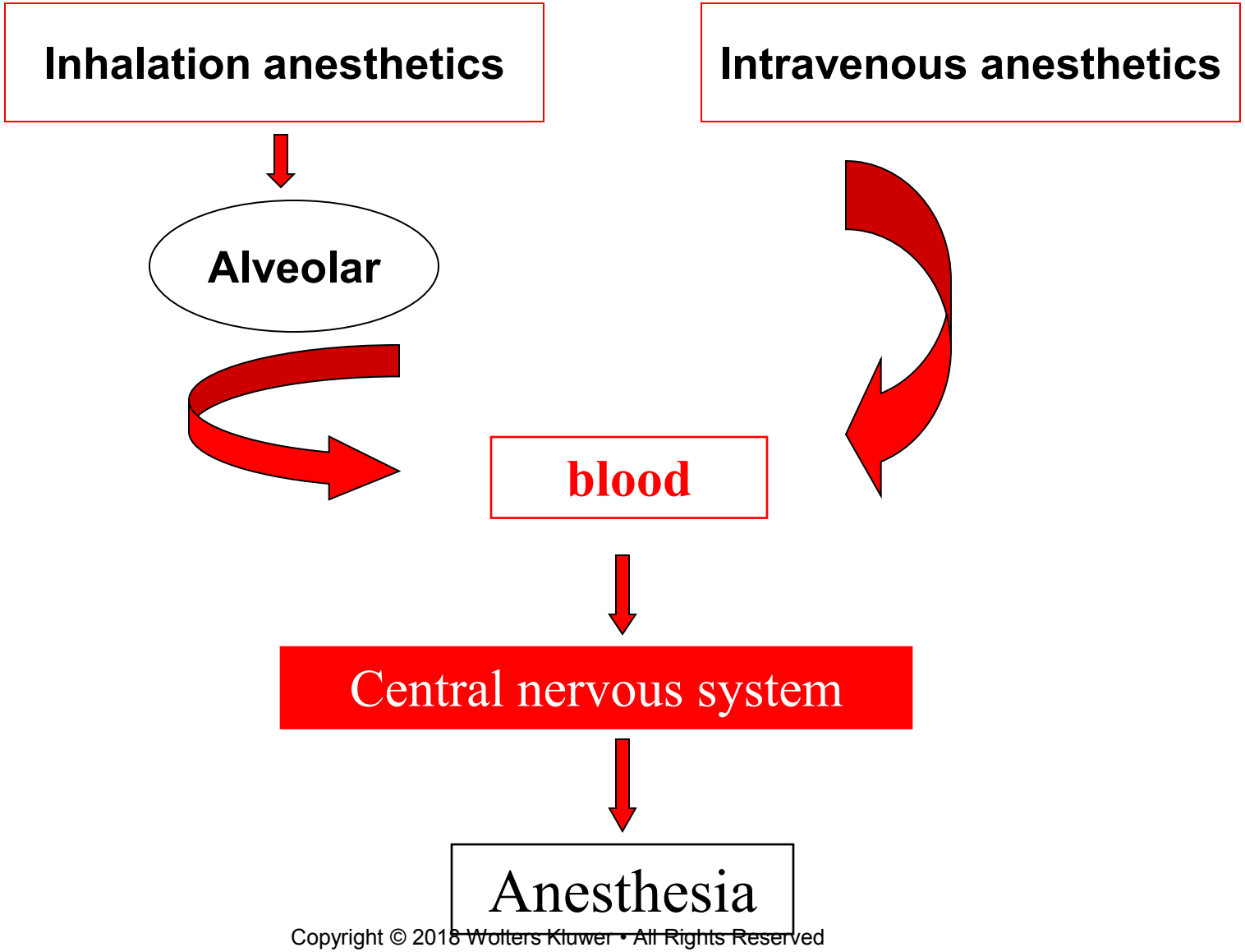
## Intravenous

- Injections
- Anesthetics or induction agents

## Inhalational

- Gasses or Vapors
- Usually Halogenated

# Route of Administration



# Intravenous Anesthetics

# Intravenous Anesthetics

Single injection to induce anesthesia

Induction » period between being conscious and unconscious

- Rapid induction of anesthesia "*arm-brain circulation time*"
- Could be used for maintenance – short surgeries – TIVA
- At low doses → sedative/hypnotic
- Mechanism of action is unknown

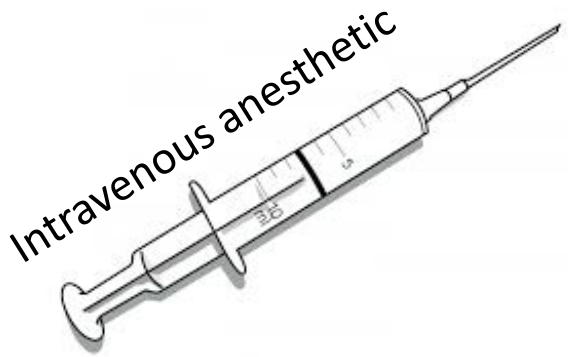
Total intravenous anesthesia

Not approved to be used outside hospital

Very difficult to control dose outside hospital (IV) » respiratory depression

# INDUCTION

Loss of consciousness / complete anesthesia » before counting to ten




They affect rate of crossing of drug of BBB 8

Free-bound ratio ↳ Only non-bound crosses

Lipid solubility

Ionization ↳ Less charged

Crosses blood brain barrier

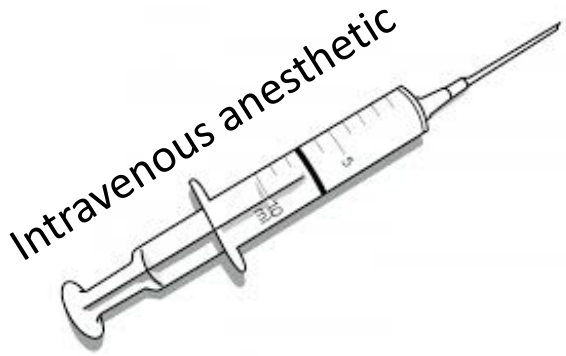
BBB

BRAIN

Permeable » simple diffusion

Cardiac output affects diffusion

# INDUCTION




Free-bound ratio
Lipid solubility
Ionization

BBB

BRAIN

Patient with hypovolemic shock or cardiac failure will decrease cardiac output » as compensatory response blood flow will be transported increasing cardiac output to the brain to increase delivery of drug to brain

Solution: reduce dose/slowly titrate!!

Tareq Saleh ©

# RECOVERY

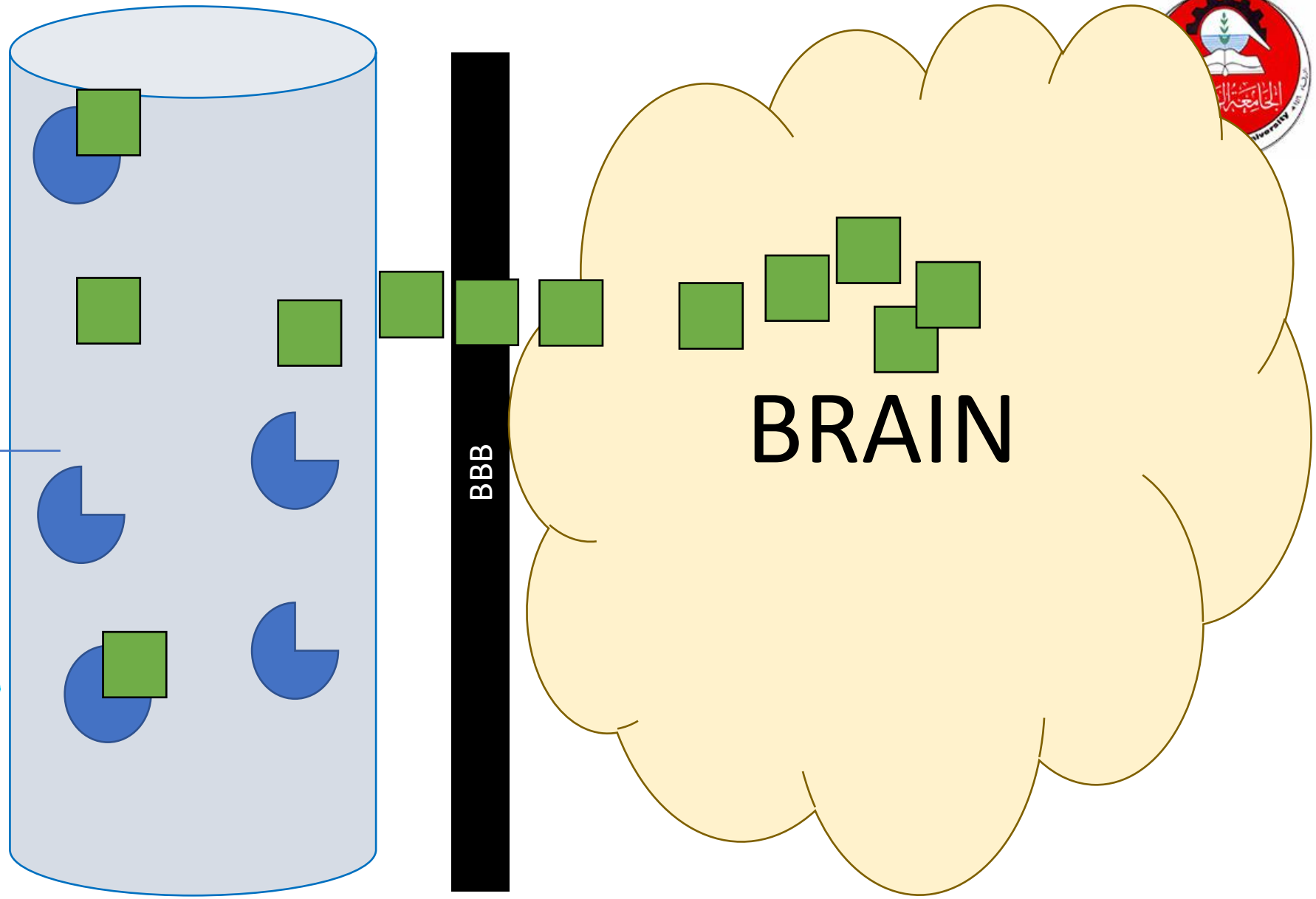
Recovery happens due to the **redistribution** rather than metabolism

Within seconds » complete shutdown of brain function

Other tissues:
Skeletal muscles, fat

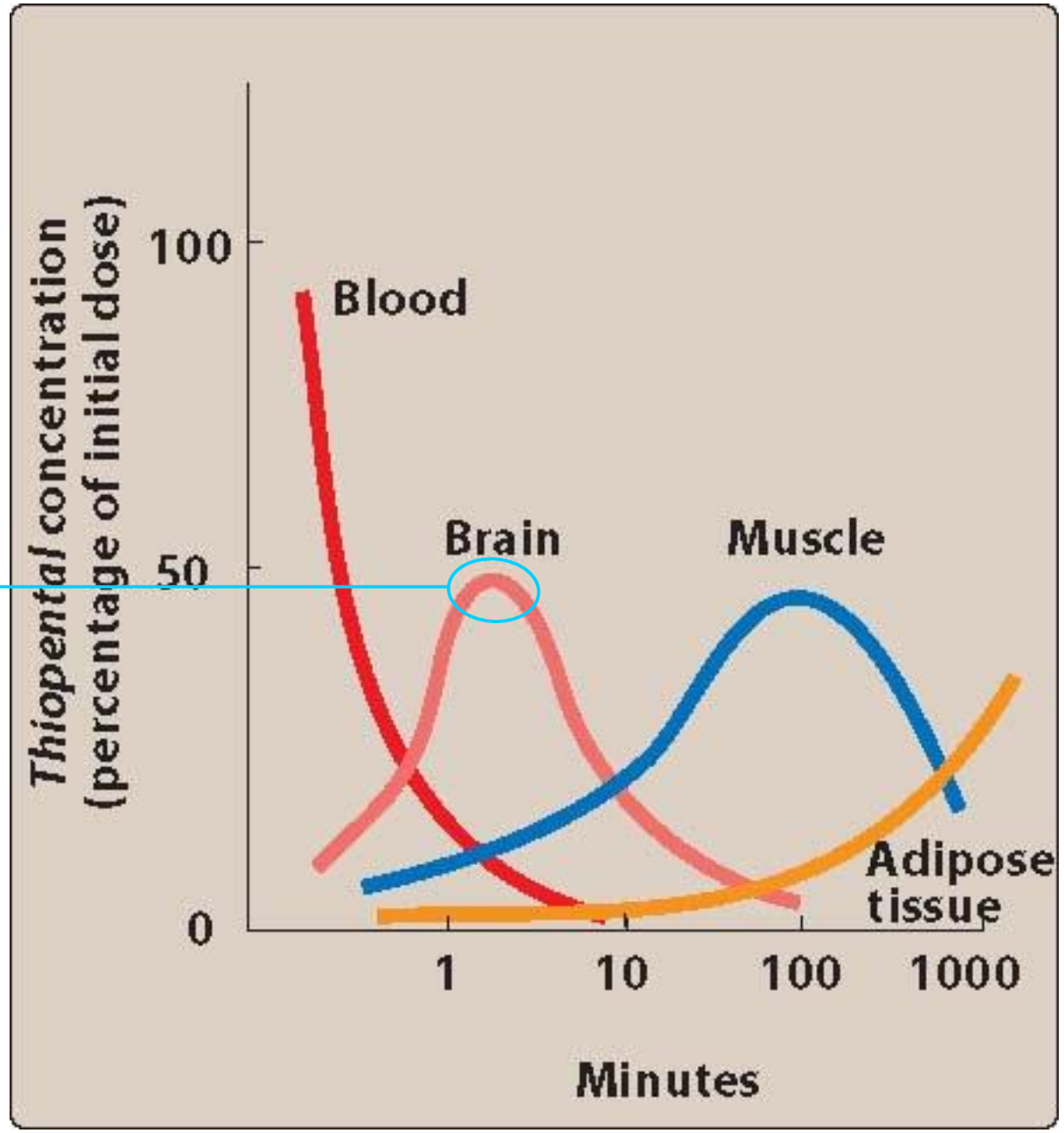
Terminated by redistribution from brain ( washed out from brain to blood)

That doesn't mean they don't undergo metabolic but it's not the method terminating it's effect



First distribution is for the brain

Peak» full complete anesthesia



# I. Propofol

- IV sedative/hypnotic
- First choice for induction of general anesthesia and sedation
- "mill-like appearance" — Highly lipid soluble, emulsified
- Induction: 30-40 seconds
- Redistribution: 2-4 minutes — Represents time of redistribution
- No analgesia — Use another anesthetic to maintain effect
- No postoperative nausea/vomiting
- decreases BP and ICP — CVS / RS depression

# II. Barbiturates (thiopental)

Very rapid acting

- Ultra-short acting barbiturate
- Induction ~ 1 minute
- Potent anesthetic – weak analgesic
- Largely replaced by propofol (no longer used in the US)

# III. Benzodiazepines (midazolam, diazepam)

- Used in adjunct with other anesthetics for their sedative/amnestic effects

For unpleasant surgeries

# IV. Opioids (fentanyl)

Morphine

Anti-depressant.

# V. Ketamine

Used with poor anesthetics

- Short-acting, non-barbiturate
- NMDA receptor antagonist

Might regain consciousness, paralyzed but can see, can't feel any stimuli

- Induces ***dissociative anesthesia*** + **analgesia**
- Cardiovascular effects: ↑ blood pressure ↑ cardiac output and bronchodilator

In patients of risk of cardiovascular prolapse

--- good for hypovolemic, cardiogenic shock, asthmatics

--- contraindicated in hypertensive, stroke

Cerebral bleeding

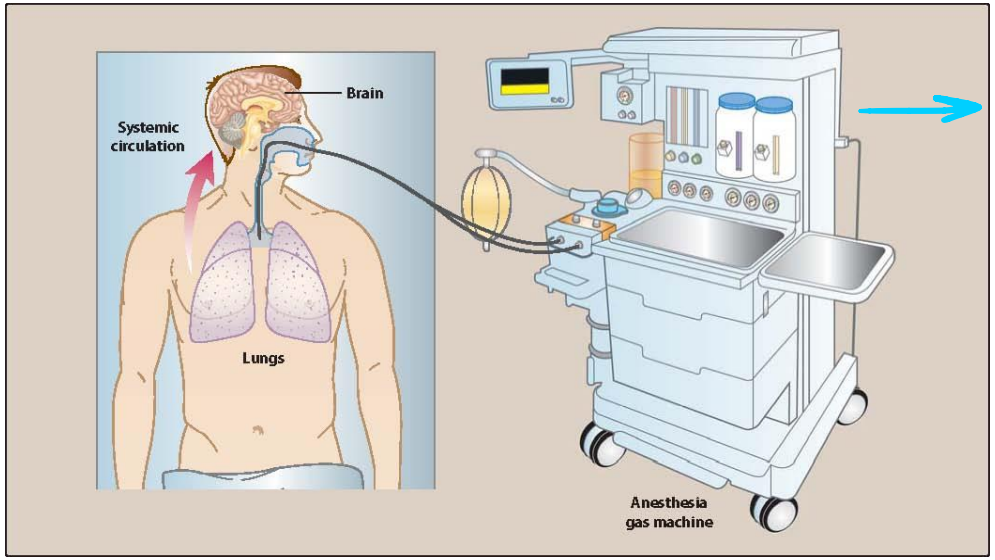
- May induce hallucinations/dream-like state

# Inhalational Anesthetics

# Inhalational Anesthetics

To maintain anesthesia » maintain delivery of gas to lungs

- Primarily used for maintenance of anesthesia following induction by IV agents.
- Depth of anesthesia correlates with inhaled concentration.
- Less risk of cardiac/respiratory depression than IV agents.
- No antagonists.

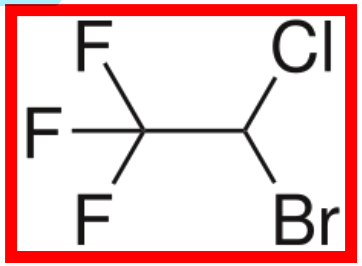



Ventilation + drug delivery

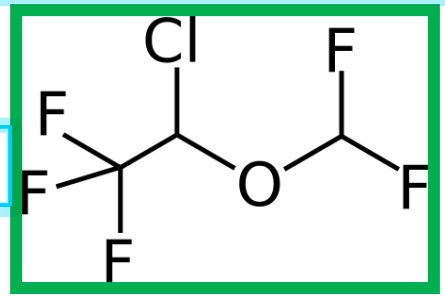
# Inhaled anesthetics

1- Halogenated(with $Cl^-$,$F^-$,$I^-$) Volatile liquids:

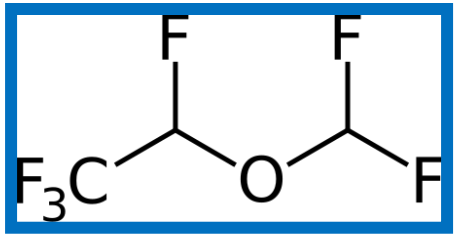
* Halothane — Not used » liver toxicity , malignant hyperthermia




* Isoflurane

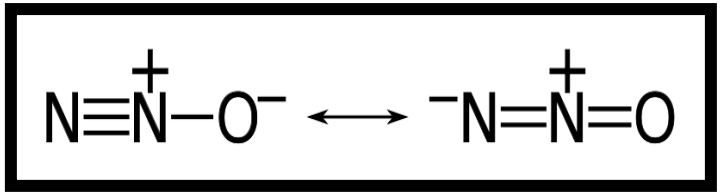



* Desflurane — Widely used » safe




* Sevoflurane

2- Gases: Nitrous oxide



# Mechanism of Action of Inhalational Anesthetics is UNKNOWN!

**Possible mechanisms:**

Increase the sensitivity of $GABA_A$ receptors to GABA

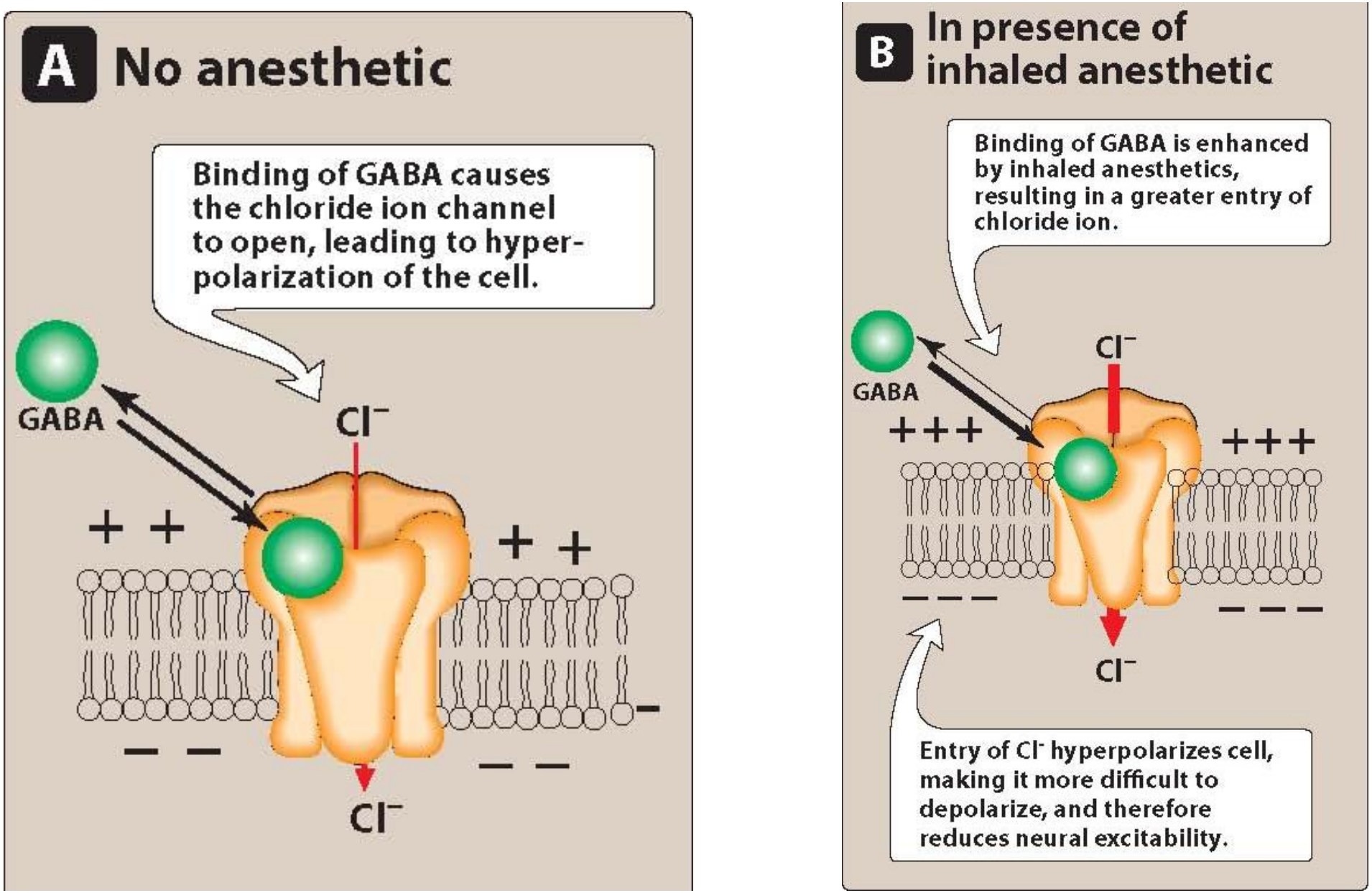
(nitrous oxide, ketamine have no effect on GABA)

Inhibition of NMDA receptors

Increase the activity of glycine receptors in the spinal chord

Block excitatory postsynaptic currents of nicotinic receptors

Overall result » depression of CNS




State of hyperpolarization

# Potency: MAC

Efficacy » depends on concentration of the drug, if drug can exert large effect with low concentration it's efficient

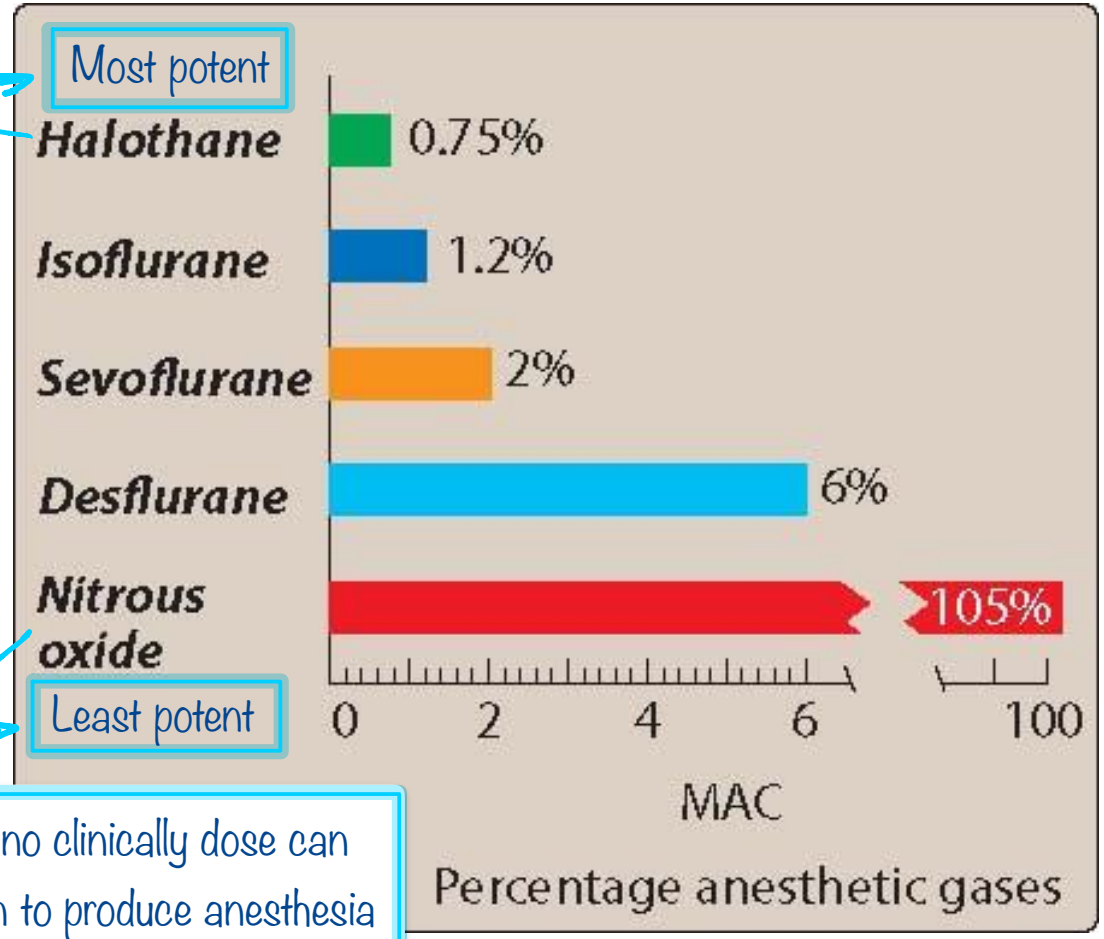
## Minimum Alveolar Concentration (MAC)

- The end-tidal concentration of an inhalational anesthetic needed to eliminate movement in 50% of patients stimulated by a standardized incision.
- MAC = $ED_{50}$ of an anesthetic

Less Mac » more potent

- MAC is expressed as percentage of alveolar gas mixture/ partial pressure as % of 760 mm of Hg.

# Potency: MAC




Almost no clinically dose can be given to produce anesthesia

Patient related factors can change Mac

↑ MAC

- Hyperthermia
- Chronic alcohol abuse
- ↑CNS catecholamines

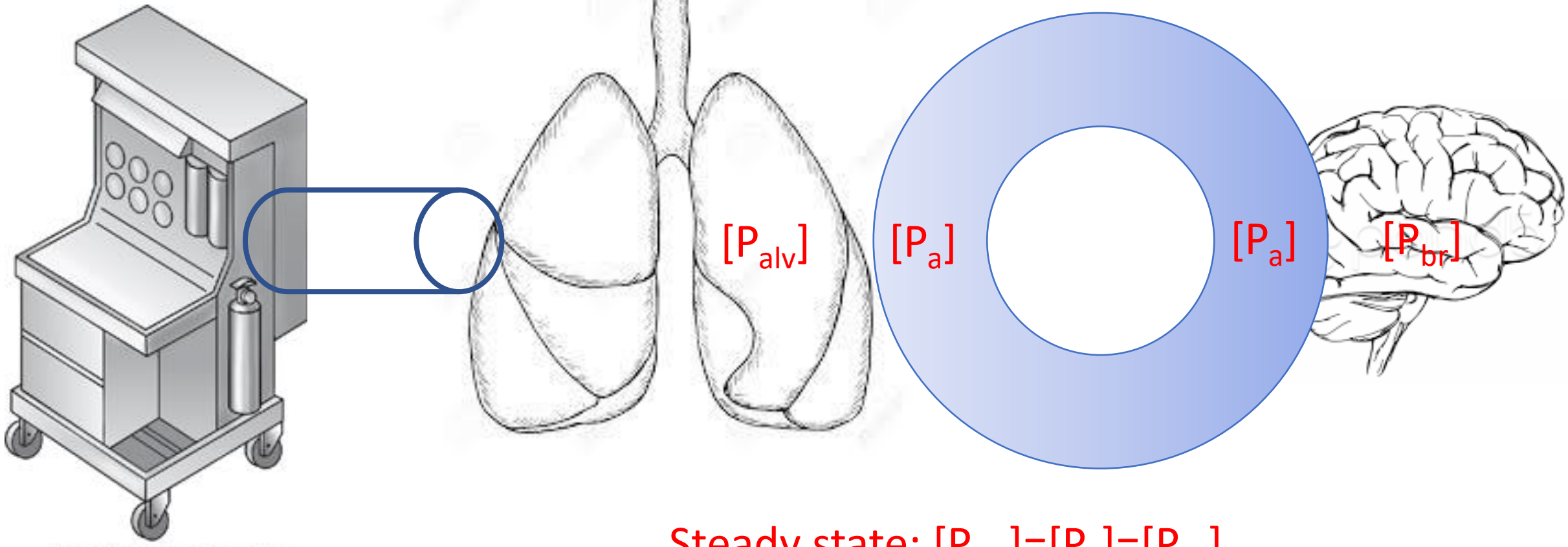
↓ MAC

- Increased age
- Hypothermia
- Pregnancy
- Sepsis
- Concurrent use of an IV anesthetic
- $\alpha_2$ agonists

# Distribution

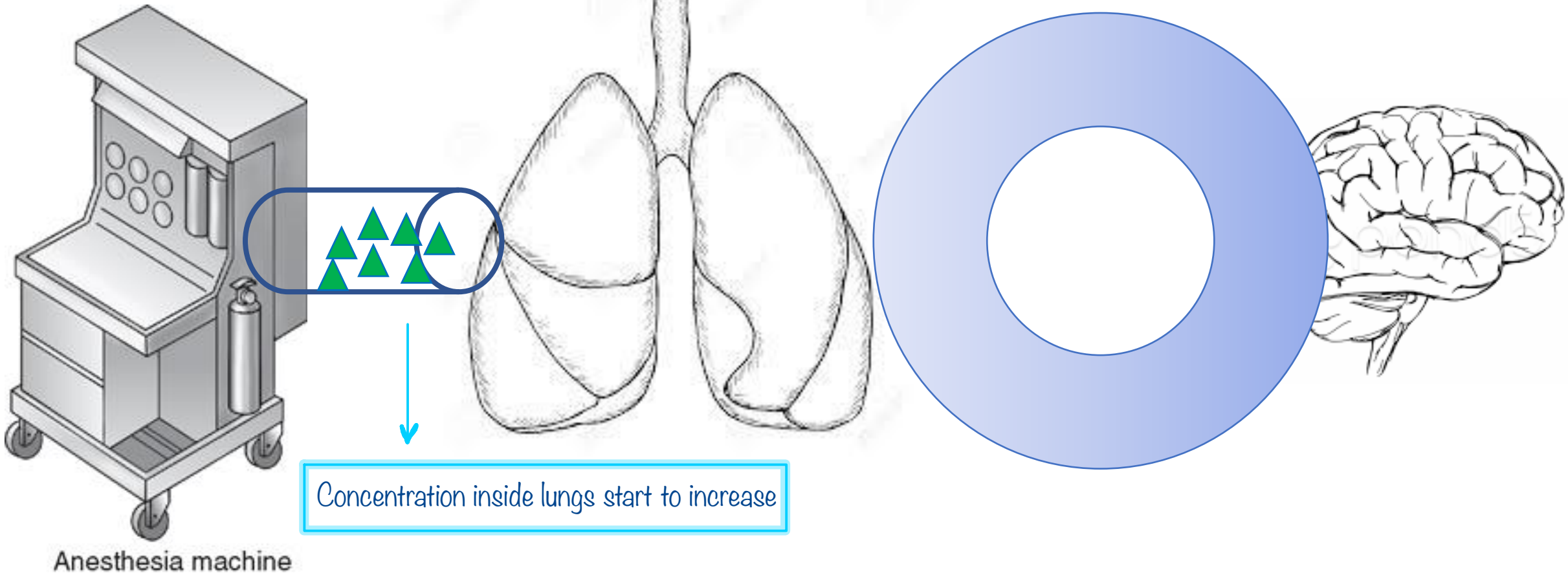
The pharmacologic effect of an inhalation agent is determined by the partial pressure of the anesthetic in the brain [$P_{br}$]

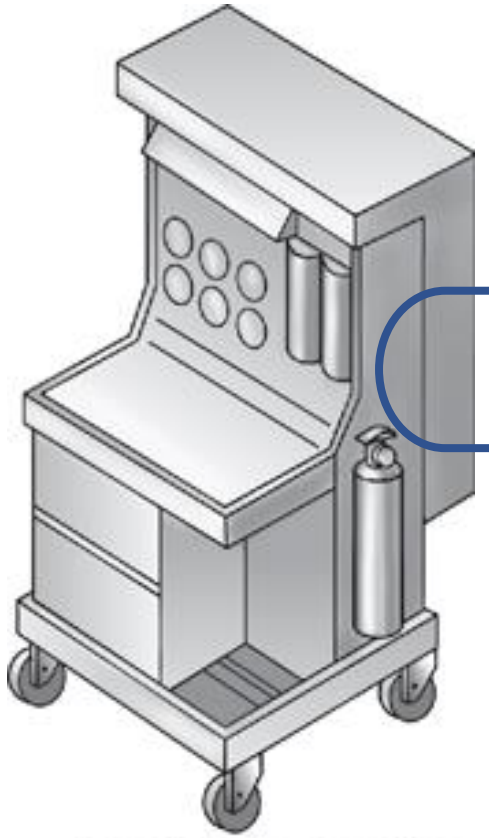
[$P_{br}$] depends on alveolar partial pressure [$P_{alv}$] which is controlled by pressure at the origin of the respiratory pathway.



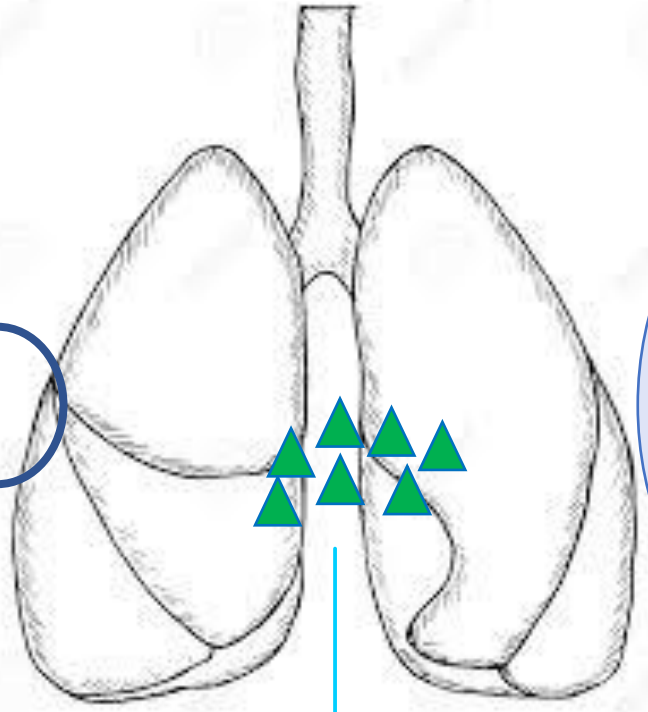

Steady state: $[P_{alv}]=[P_a]=[P_{br}]$

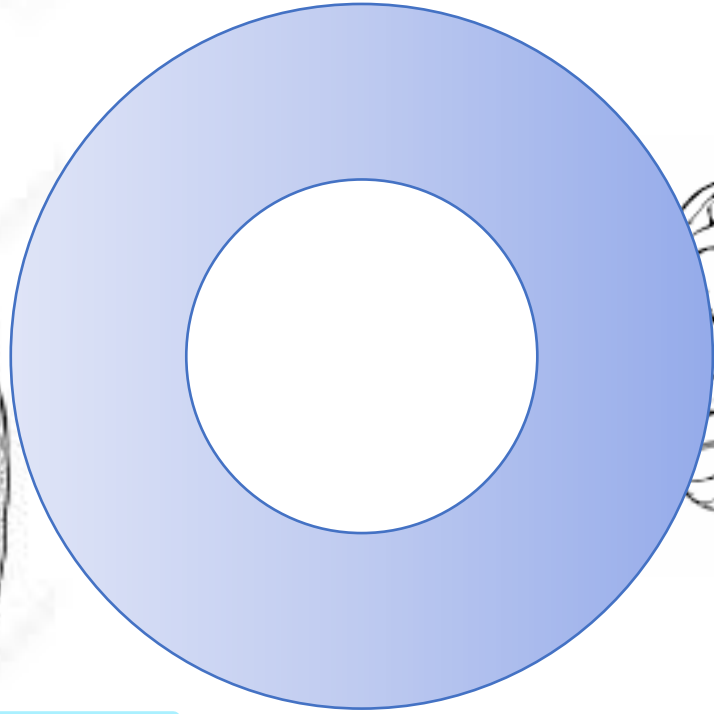
Equilibrium produces maintain

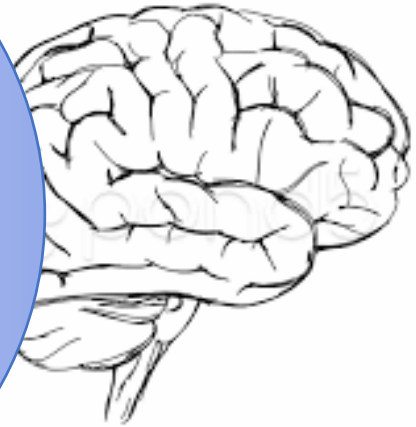




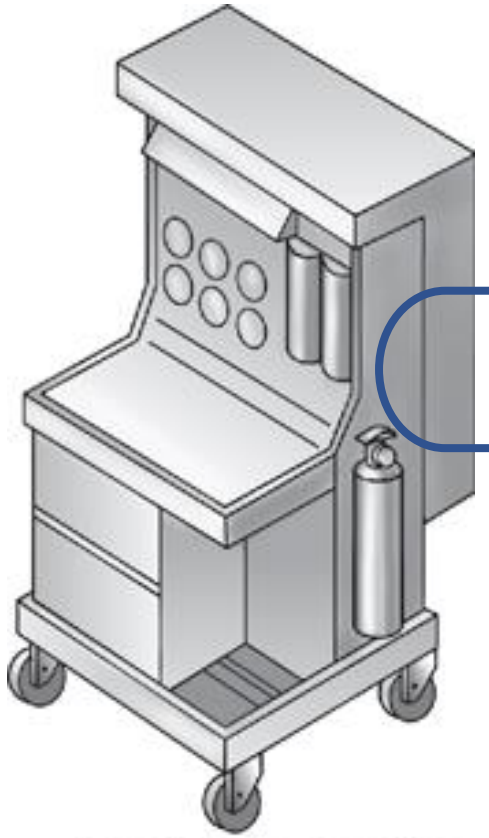
Anesthesia machine



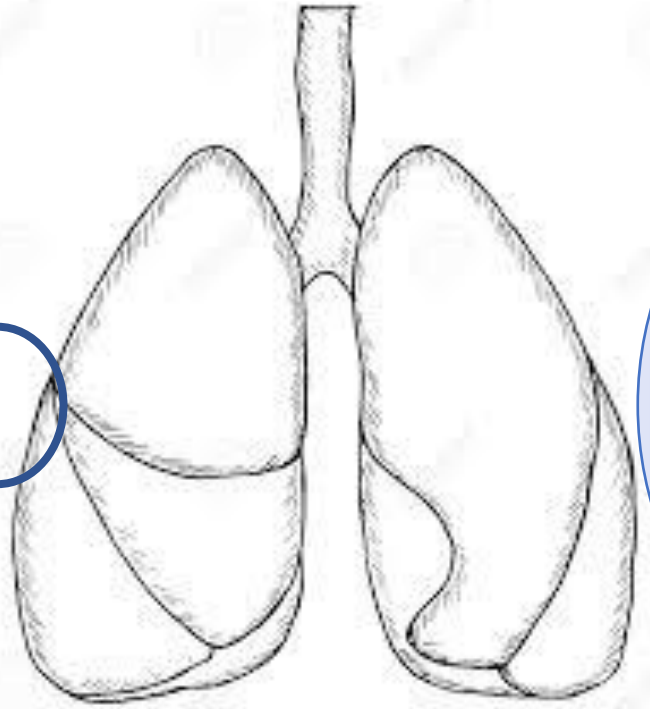


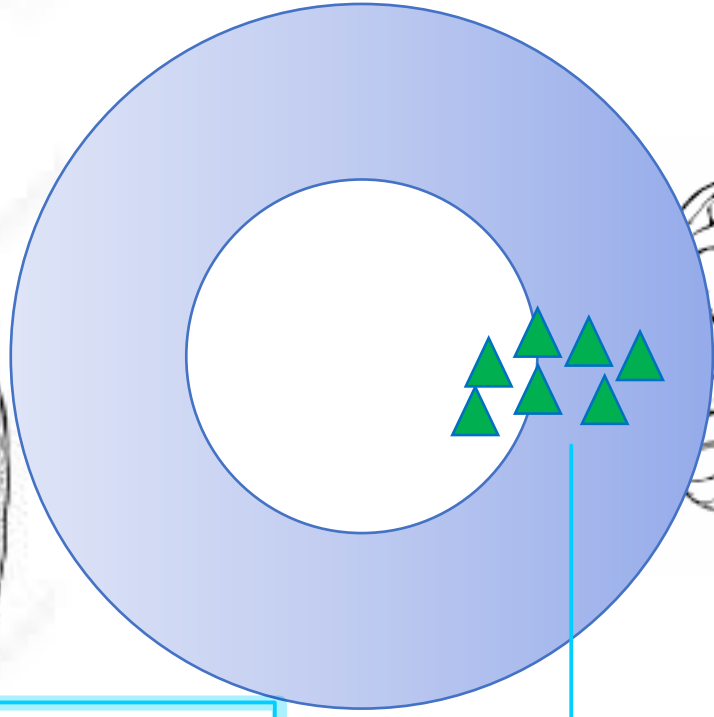


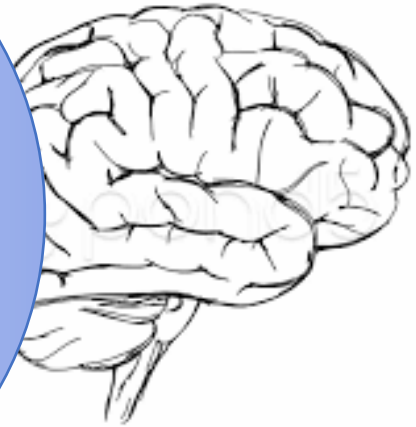
هون راح ينتقل الغاز من التركيز الاعلى ل الاقل يعني من الرئة للدم



Anesthesia machine





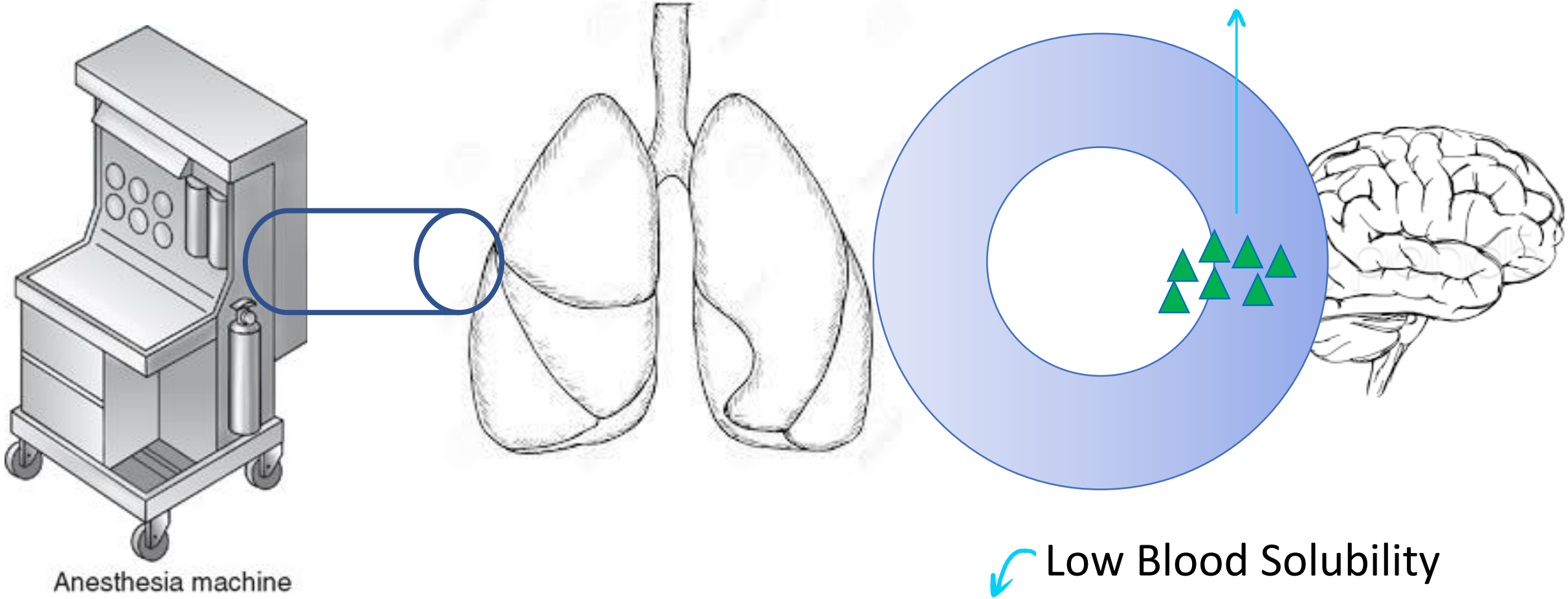


و هون راح ينتقل الغاز من التركيز الاعلى للاقل يعني من الدم للدماغ

High Blood Solubility

High blood solubility » low lipid solubility » low brain diffusion rate » more time to produce effect

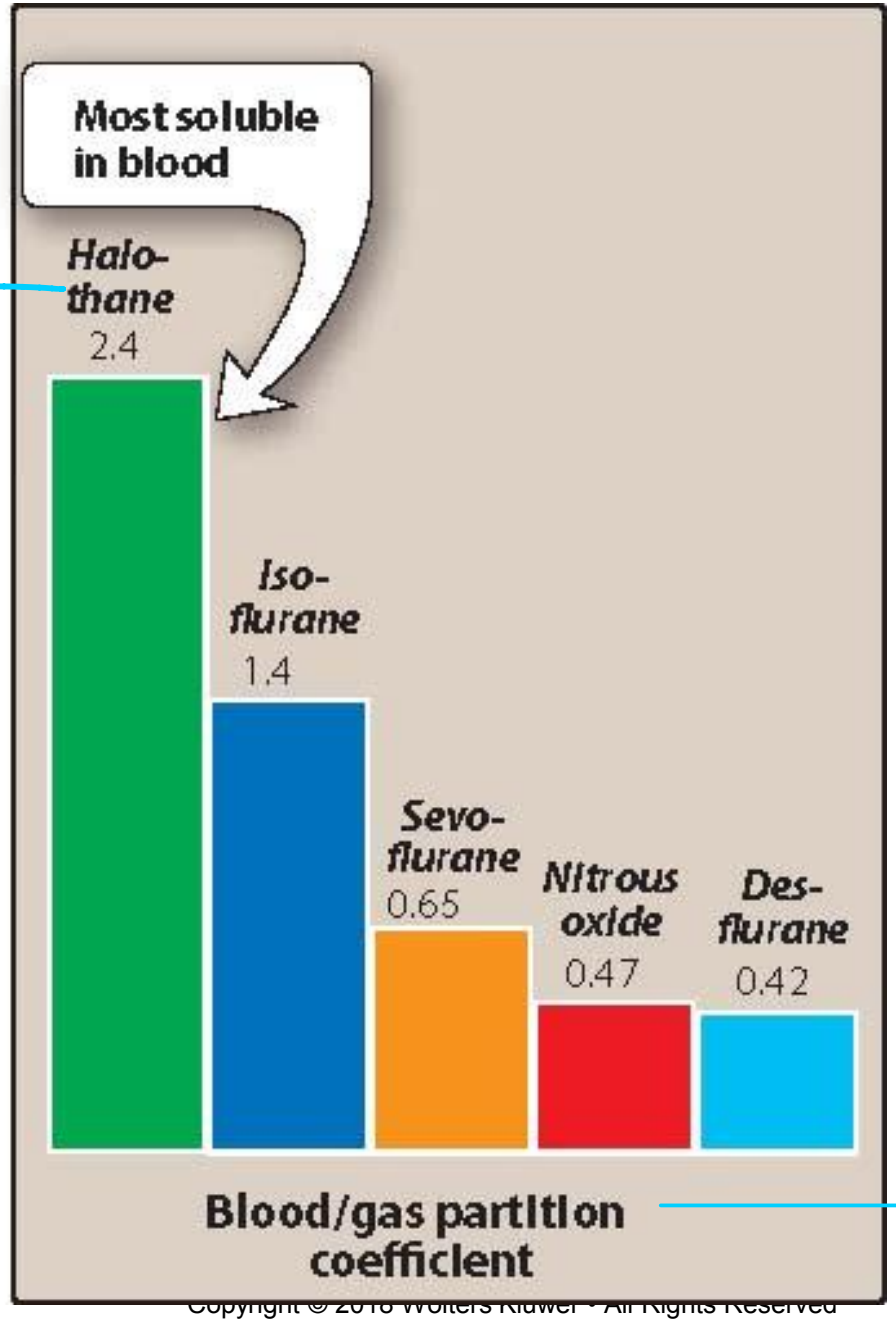
اذا قل التركيز بالدم الغاز راح يصير يطلع من الدماغ الي هو منطقة التركيز الاعلى و يروح للدم الي هو بهاي الحالة منطقة التركيز الاقل و هيك بقل تاثير الغاز على المريض زي ما حكينا عن طريق ال redistribution




Low Blood Solubility

High lipid solubility » high brain diffusion rate » lesstime to produce effect

بطيء ← ال recovery تاعته بطيئة
← بطول ليطلع من الدم

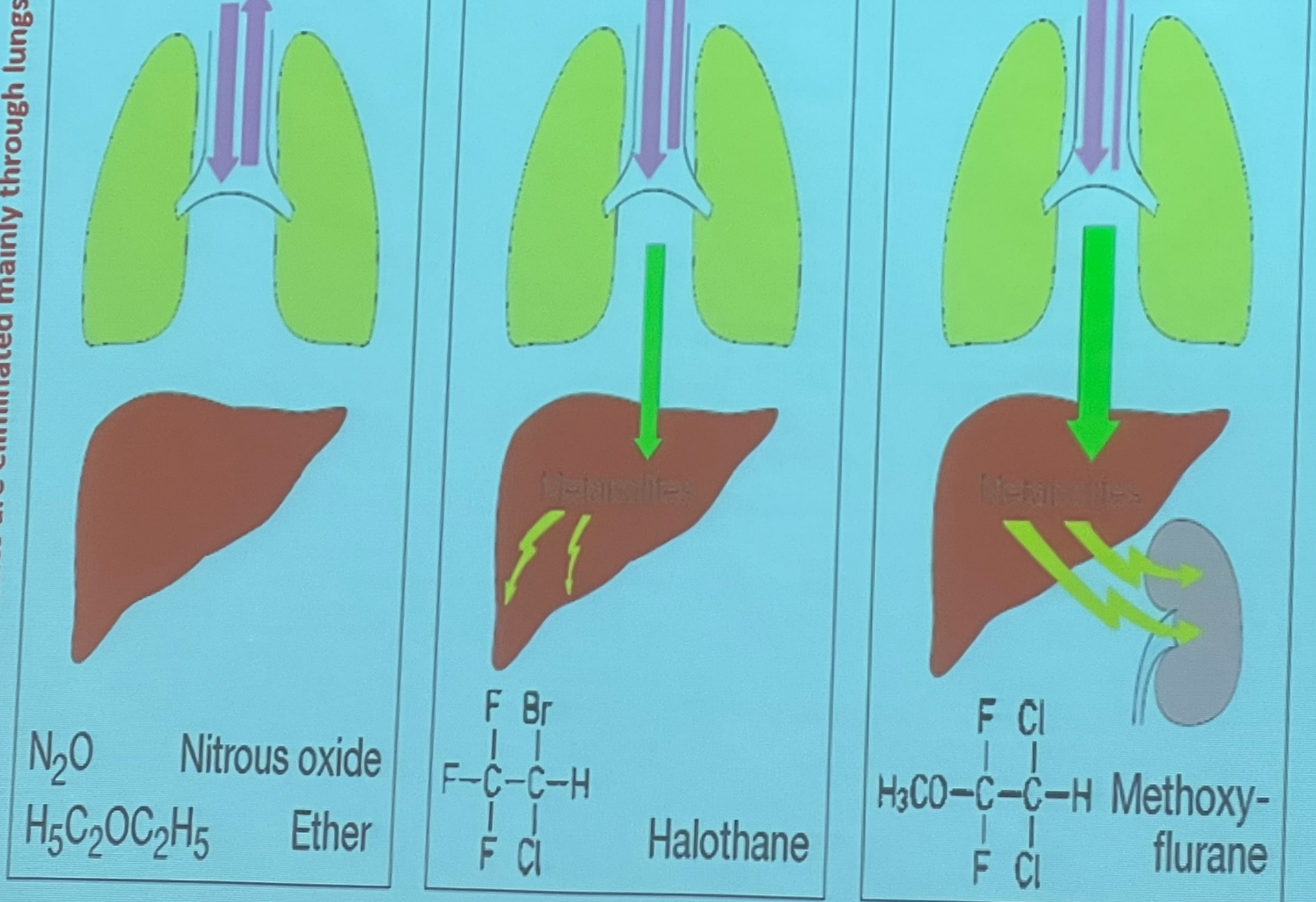



ال MAC بتقيس ال potency يعني قوته بال induction of anaesthesia

ال blood/gas coefficient بقيس ال rate كم هو سريع او بطيء بال induction or recovery from anaesthesia

كل ما كان اعلى ← الذوبان بالدم اعلى ← ابطئ بالتخدير

All inhaled anesthetics are eliminated mainly through lungs



$N_2O$ Nitrous oxide

$H_5C_2OC_2H_5$ Ether



Halothane

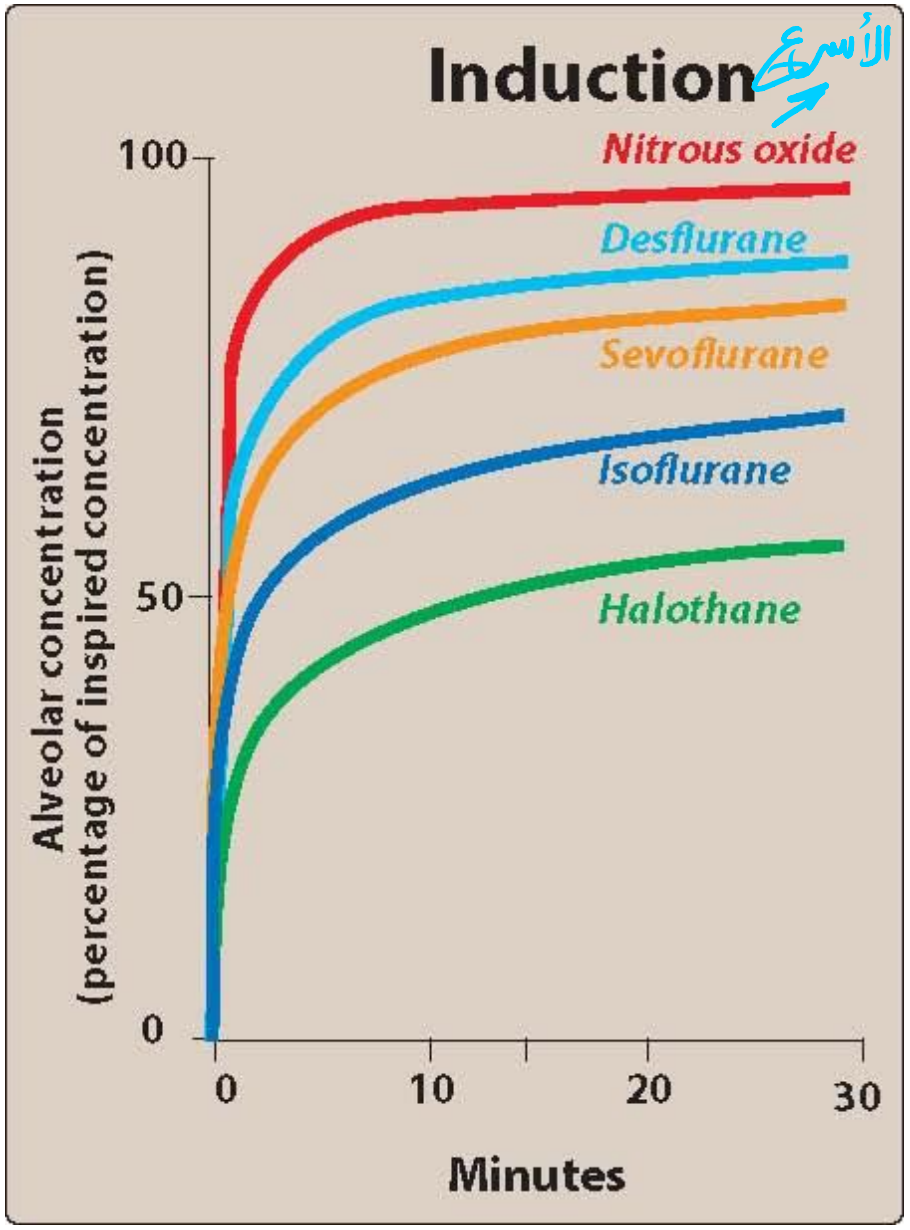


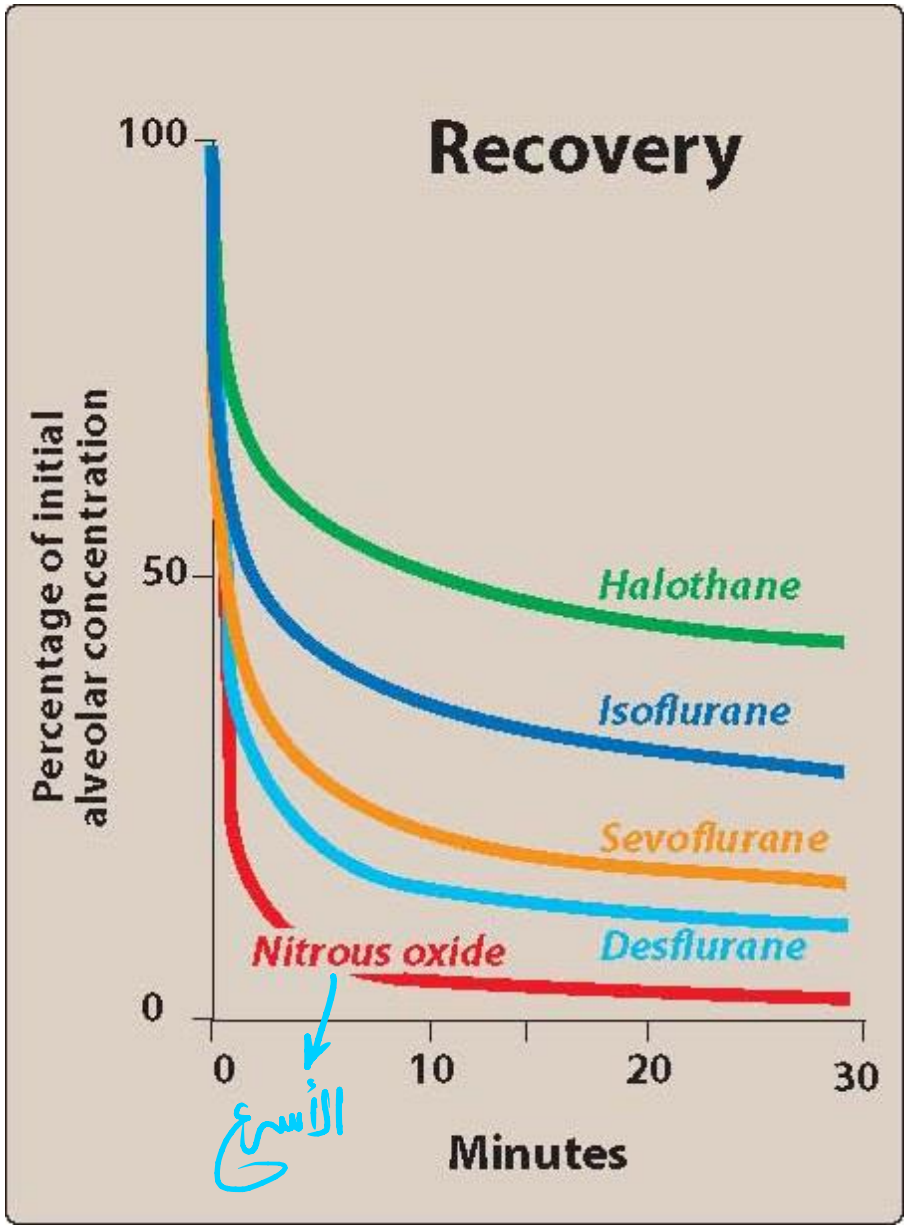
Methoxy-flurane

# Recovery

- The duration of exposure to the anesthetic can have a marked effect on the time of recovery. If exposure to the anesthetic is short, recovery may be rapid.

- Clearance of inhaled anesthetics by the lungs into the expired air is the major route of their elimination from the body



# Isoflurane

- Has a pungent smell → stimulates the respiratory reflexes → NOT used for inhalational induction
- Causes hypotension
- Solubility? Induction time?
- Low cost
- Longer surgeries

# Desflurane

- Respiratory irritant → NOT used for inhalational induction
- Causes hypotention
- Low blood solubility
- Higher cost
- Better for short surgeries

# Sevoflurane

More tolerable

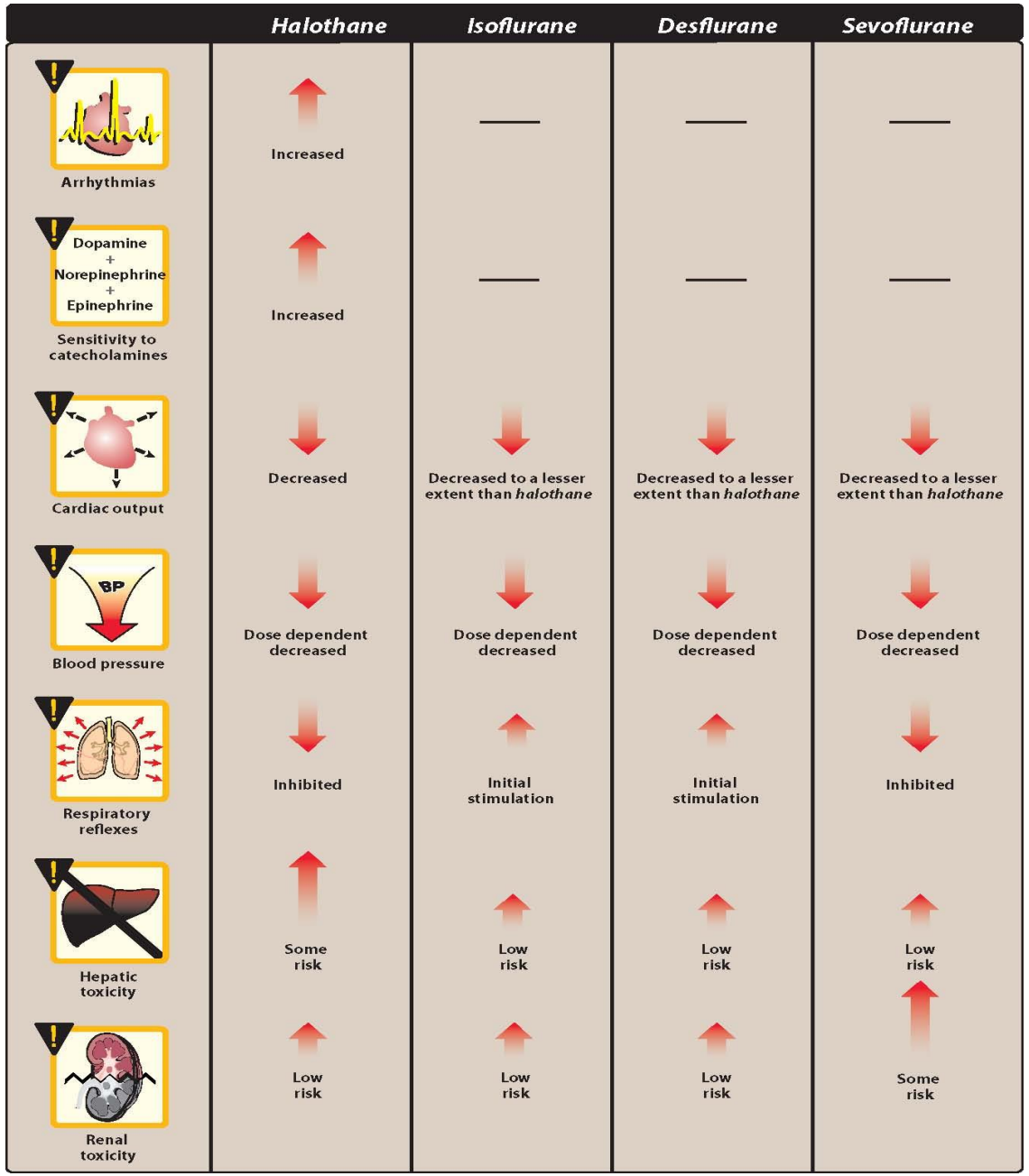
- Low pungency and respiratory irritation → can be used for inhalational induction
- Low solubility

Especially in children

# Nitrous Oxide

# Nitrous Oxide

- Gas
- Very rapid induction and recovery.
  - Why?
- least potent, highest MAC value.
- Poor anesthetic, good analgesic → Mostly used by dentist
- Administered with $O_2$ to avoid diffusion hypoxia (to produce sedation - dentistry)
- Administered with other inhalational agents for general anesthesia



# Malignant Hyperthermia

- Rare anesthesia complication (only in susceptible patients; autosomal dominant)
- Exposure to: halogenated anesthetics, succinylcholine
- Life threatening
- Due to uncontrolled, excessive increase in skeletal muscle oxidative metabolism
- Treatment: dantrolene

Muscle relaxant to facilitate intubation

اخر ١٠ سلايدات من المحاضرة ما شرحهم لسا راح انزل المحاضرة بدونهم عشان ما تتاخروا بالدراسة