Anesthetics

Pharmacology and Toxicology

Central Nervous System Module

Third Year Medical Students

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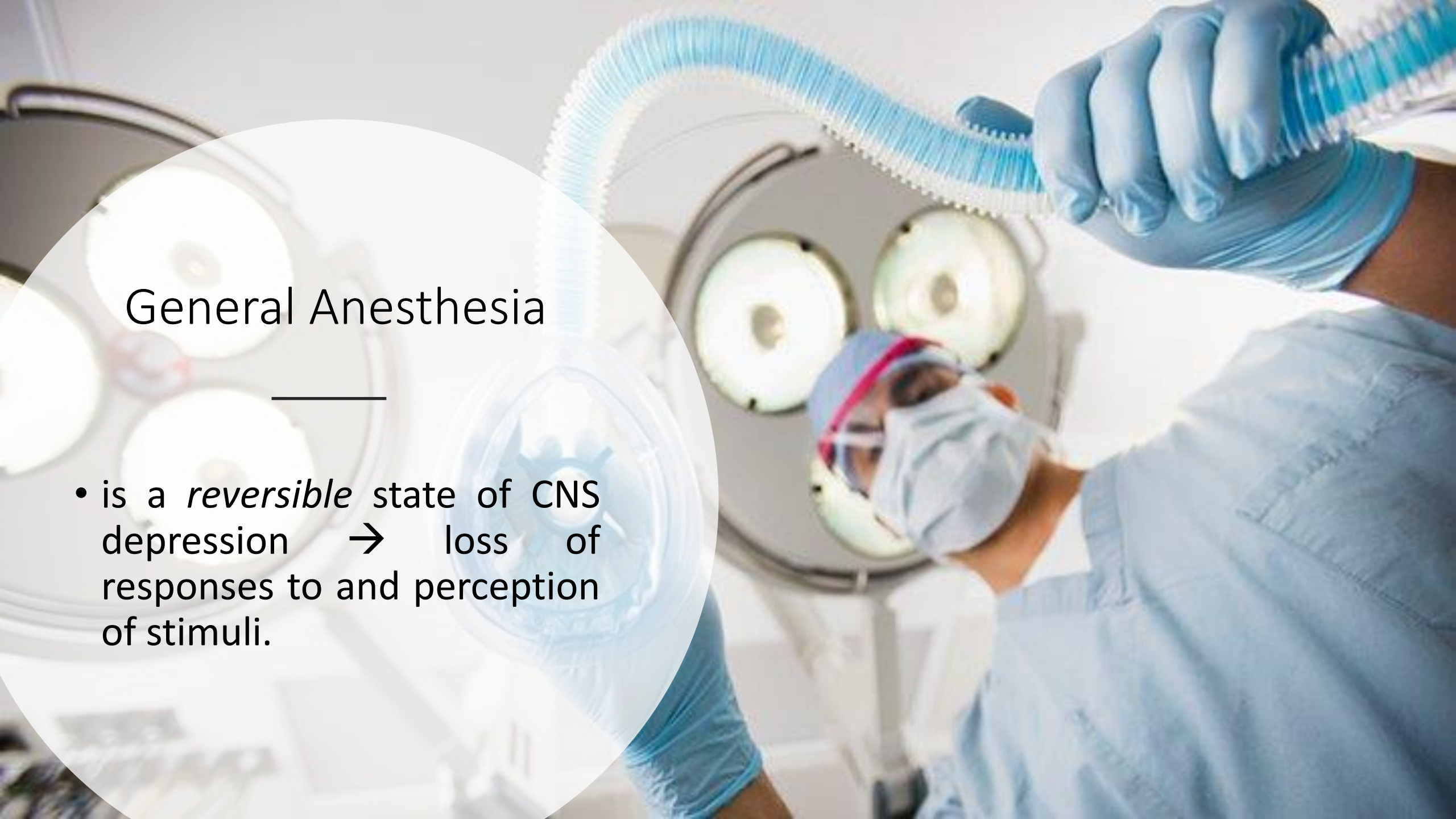
General Anesthesia

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



Why are they “general”?

- **Sensory**
  - -Absence of intraoperative pain
- **Cognitive**:
  - -Absence of intraoperative awareness
  - -Absence of recall of intraoperative events
- **Motor**:
  - -Absence of movement
  - -Adequate muscular relaxation
- **Autonomic**:
  - -Absence of hemodynamic response
  - -Absence of tearing, flushing, sweating, and gastric secretions

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
- produces analgesia, suppresses reflexes and produces muscle relaxation
- minimal cardiovascular and respiratory side effects
- cheap and easy to manufacture and administer

NO SINGLE DRUG HAS ALL THESE CHARACTERISTICS!

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

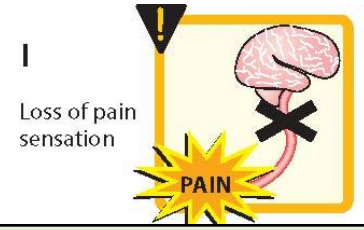
Nervous

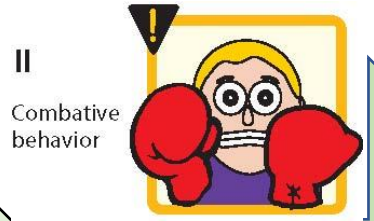
- Pre-existing neurological disorders e.g., epilepsy, myasthenia gavis

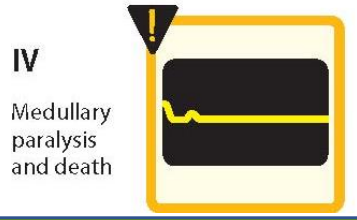
Gestational

- 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

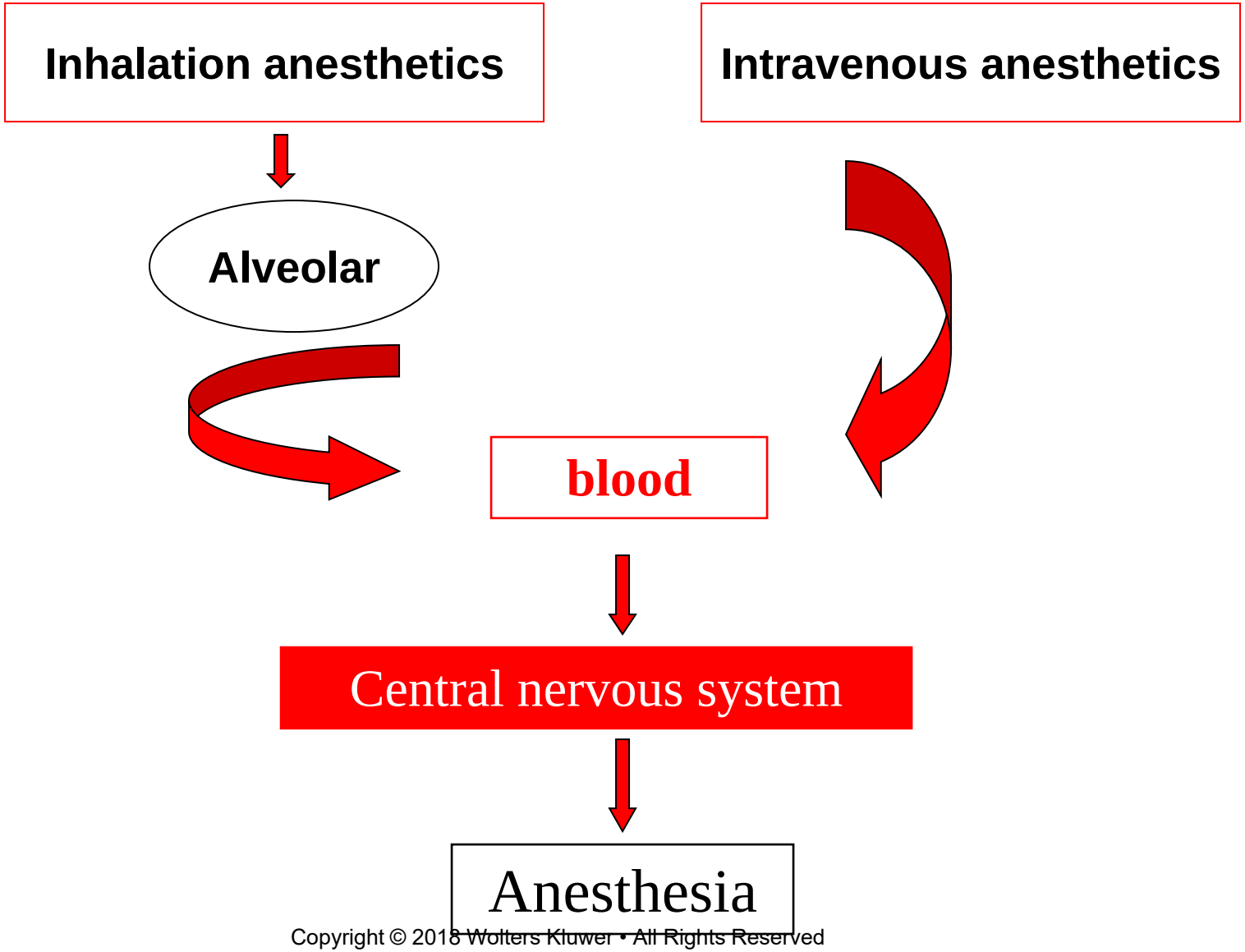
Intravenous

- Injections
- Anesthetics or induction agents

Inhalational

- Gasses or Vapors
- Usually Halogenated

Route of Administration

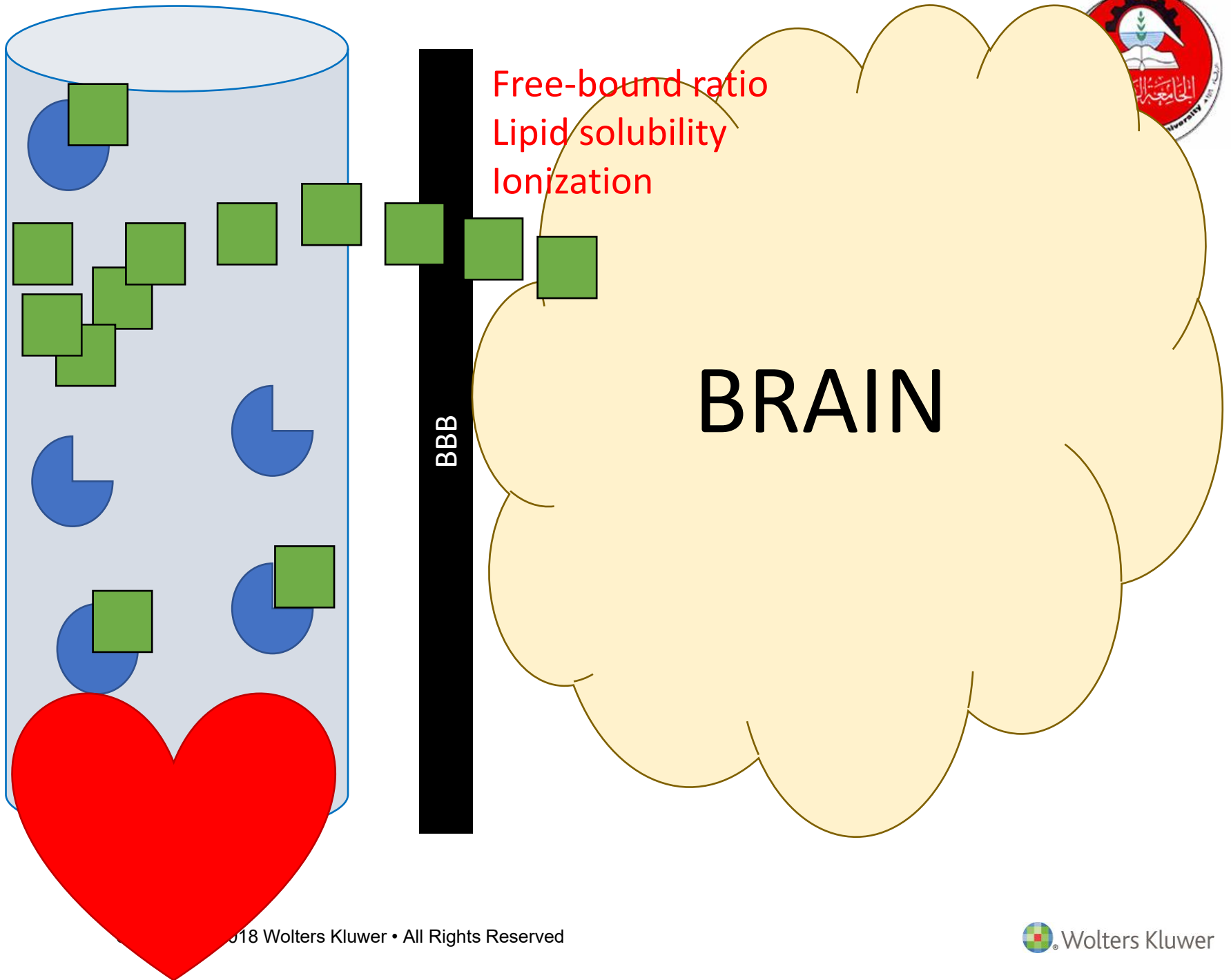


Intravenous Anesthetics

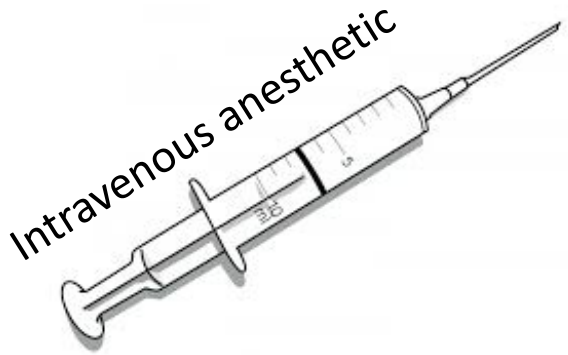
Intravenous Anesthetics

- 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 <u>unknown</u>

INDUCTION



INDUCTION



Free-bound ratio
Lipid solubility
Ionization

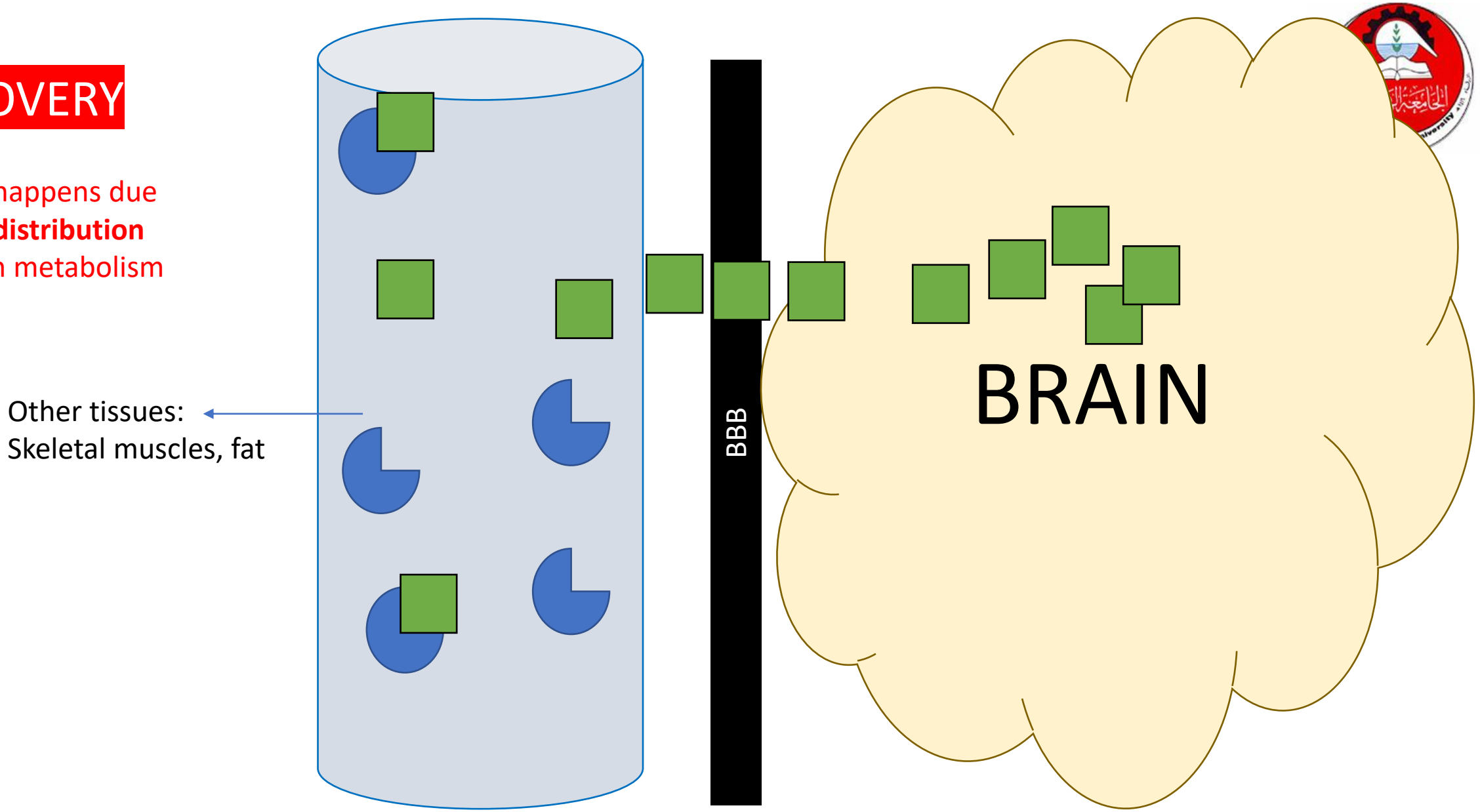
BBB

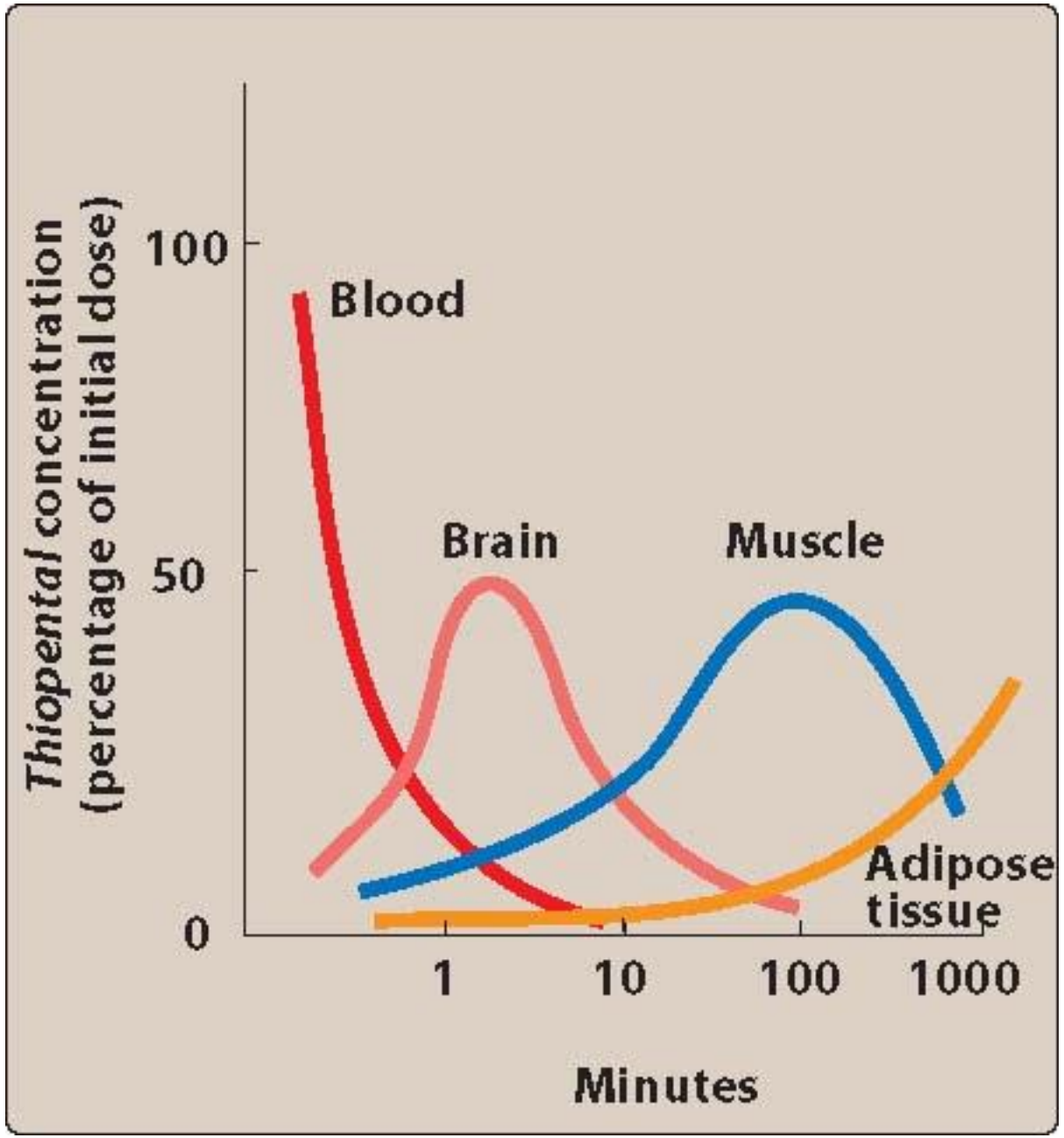
BRAIN

Solution: reduce dose/slowly titrate!!

RECOVERY

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





I. Propofol

- IV sedative/hypnotic
- First choice for induction of general anesthesia and sedation
- “mill-like appearance”
- Induction: 30-40 seconds
- Redistribution: 2-4 minutes
- No analgesia
- No postoperative nausea/vomiting
- decreases BP and ICP

II. Barbiturates (thiopental)

- 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

IV. Opioids (fentanyl)

V. Ketamine

- Short-acting, non-barbiturate
- NMDA receptor antagonist
- Induces ***dissociative anesthesia*** + **analgesia**
- Cardiovascular effects: ↑ blood pressure ↑ cardiac output and bronchodilator

--- good for hypovolemic, cardiogenic shock, asthmatics

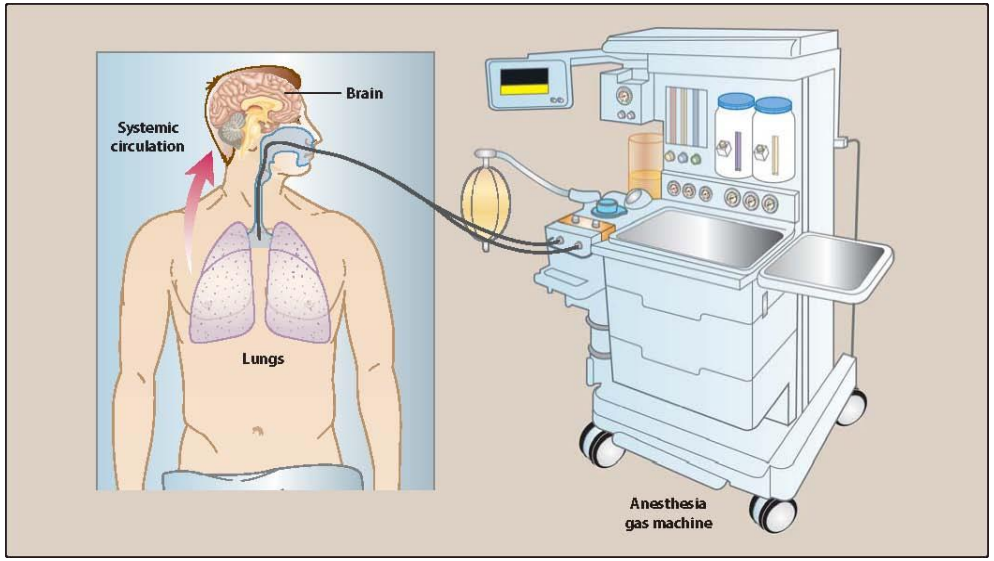
--- contraindicated in hypertensive, stroke

- May induce hallucinations/dream-like state

Inhalational Anesthetics

Inhalational Anesthetics

- Primarily used for <u>maintenance</u> 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.

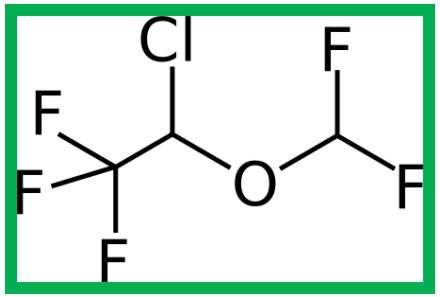


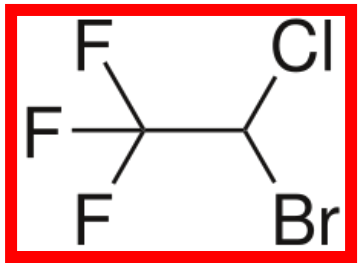
Inhaled anesthetics

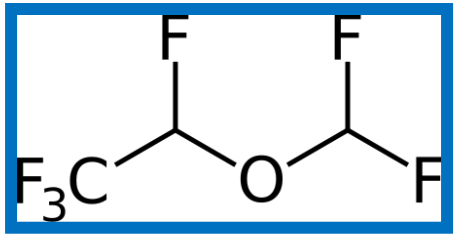
1- Halogenated(with Cl^-,F^-,I^-) Volatile liquids:

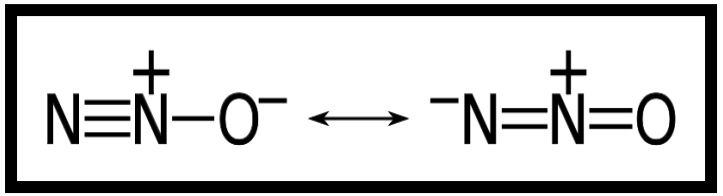
* Halothane
* Isoflurane
* Desflurane
* Sevoflurane

2- Gases: Nitrous oxide









Mechanism of Action of Inhalational Anesthetics is UNKNOWN!

Possible mechanisms:

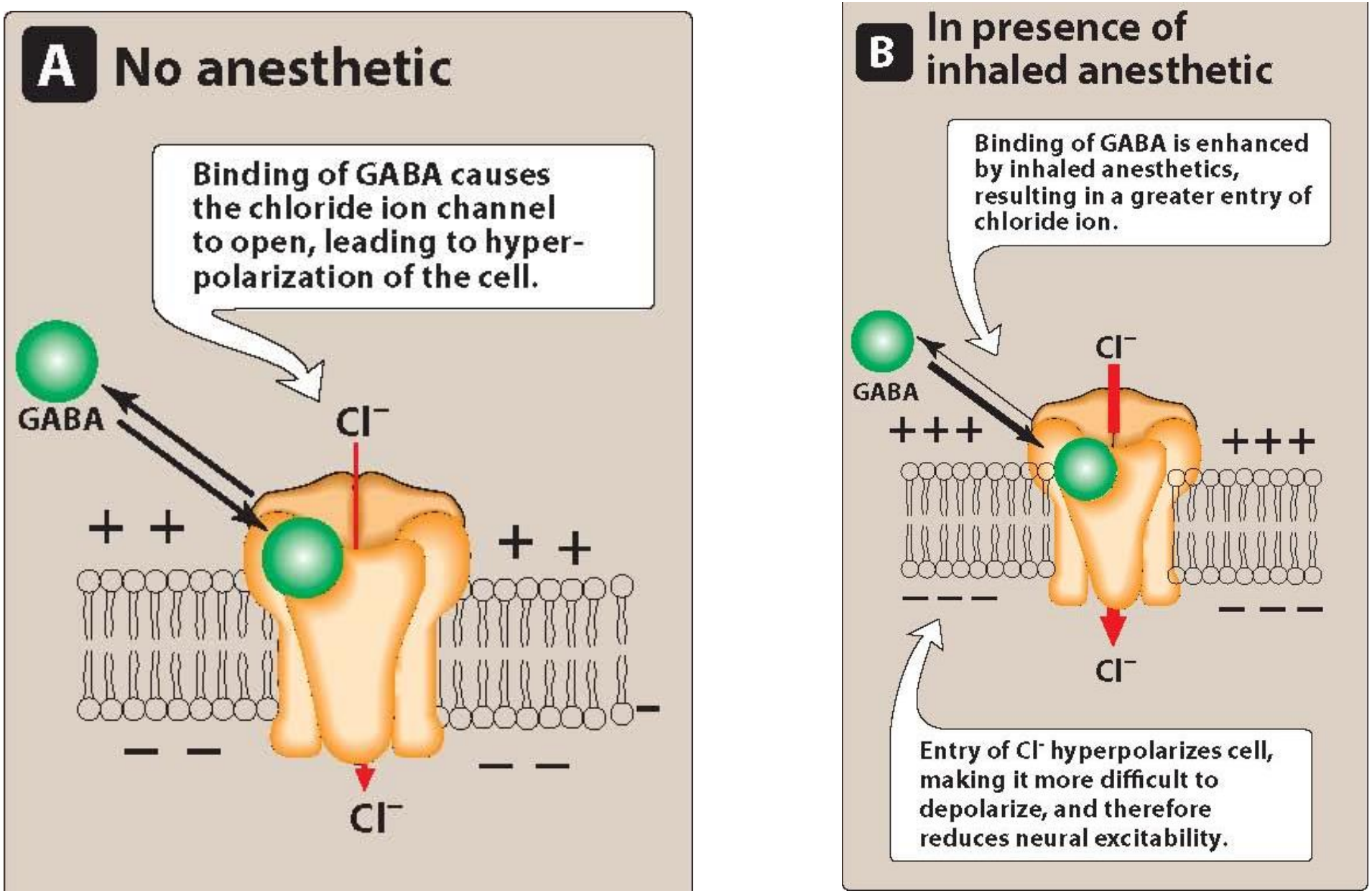
Increase the sensitivity of $GABA_A$ receptors to GABA

(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

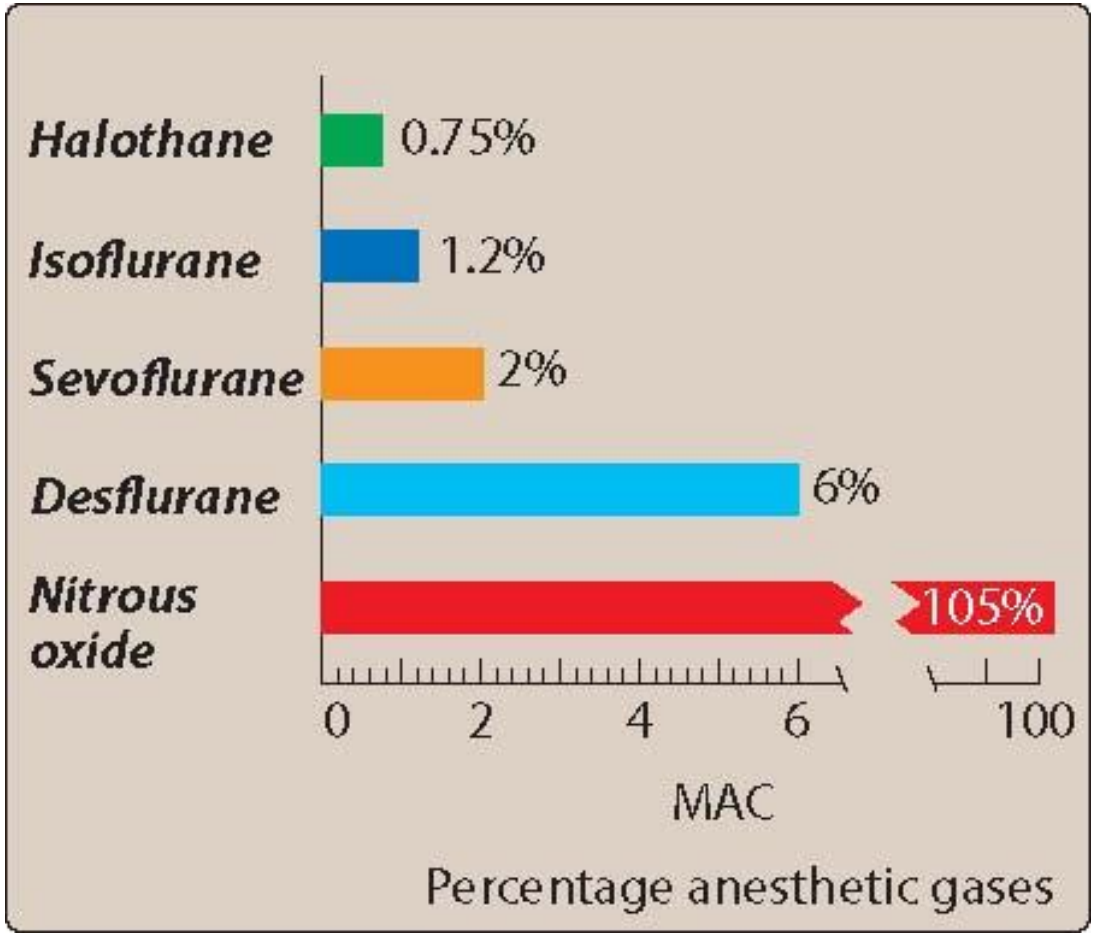


Potency: MAC

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

Potency: MAC



↑ MAC

- Hyperthermia
- Chronic alcohol abuse
- ↑CNS catecholamines

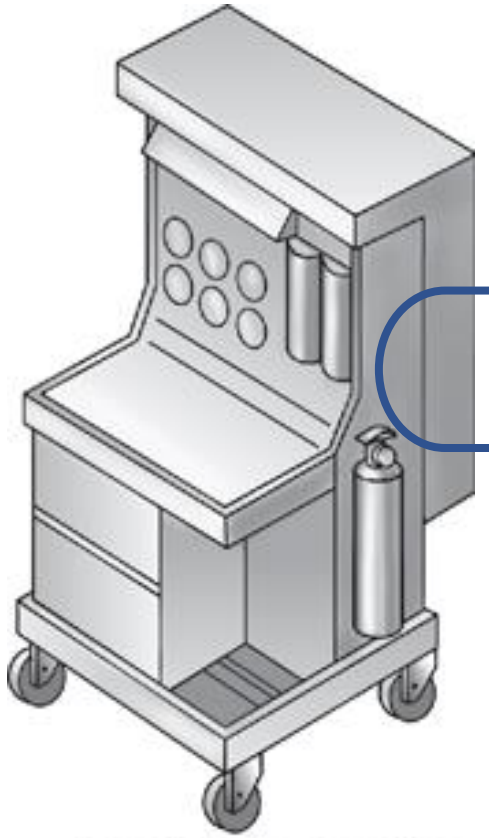
↓ MAC

- Increased age
- Hypothermia
- Pregnancy
- Sepsis
- Concurrent use of an IV anesthetic
- α_2 agonists

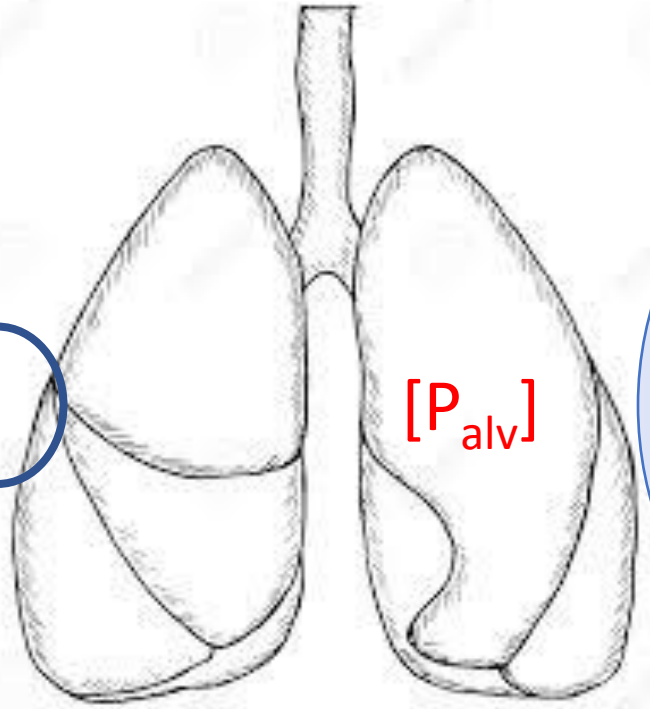
Distribution

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

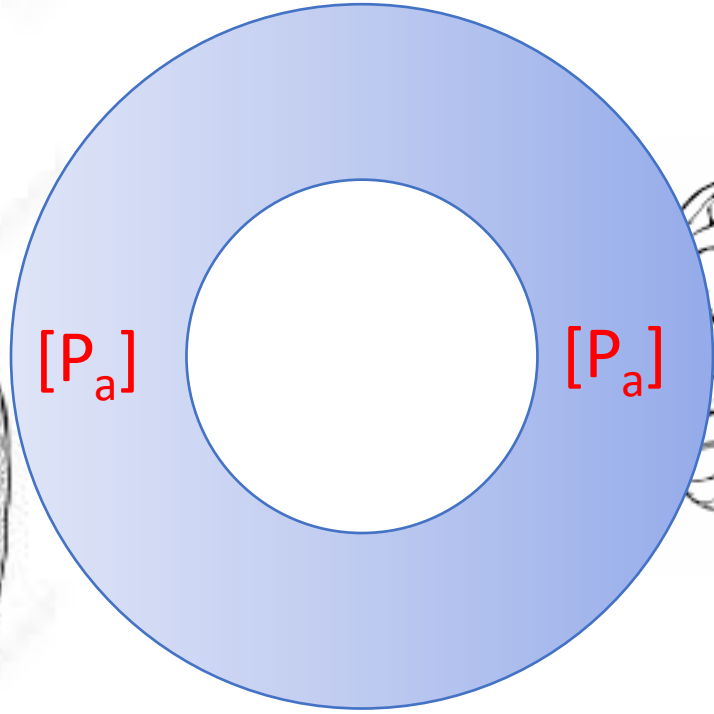
[P_{br}] depends on alveolar partial pressure [P_{alv}] which is controlled by pressure at the origin of the respiratory pathway.



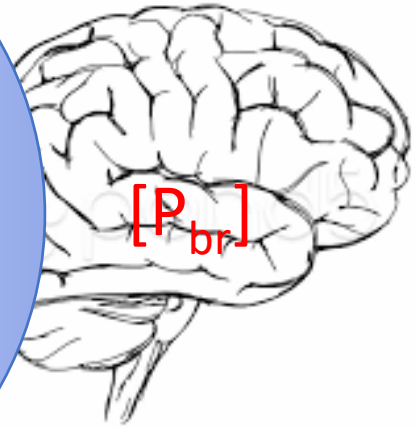
Anesthesia machine



$[P_{alv}]$



$[P_a]$ $[P_a]$



$[P_{br}]$

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

Factors affecting equilibrium/steady state

I. Alveolar Wash-In

"Replacement of normal lung gases with inspired anesthetic mixture"

II. Anesthetic Uptake

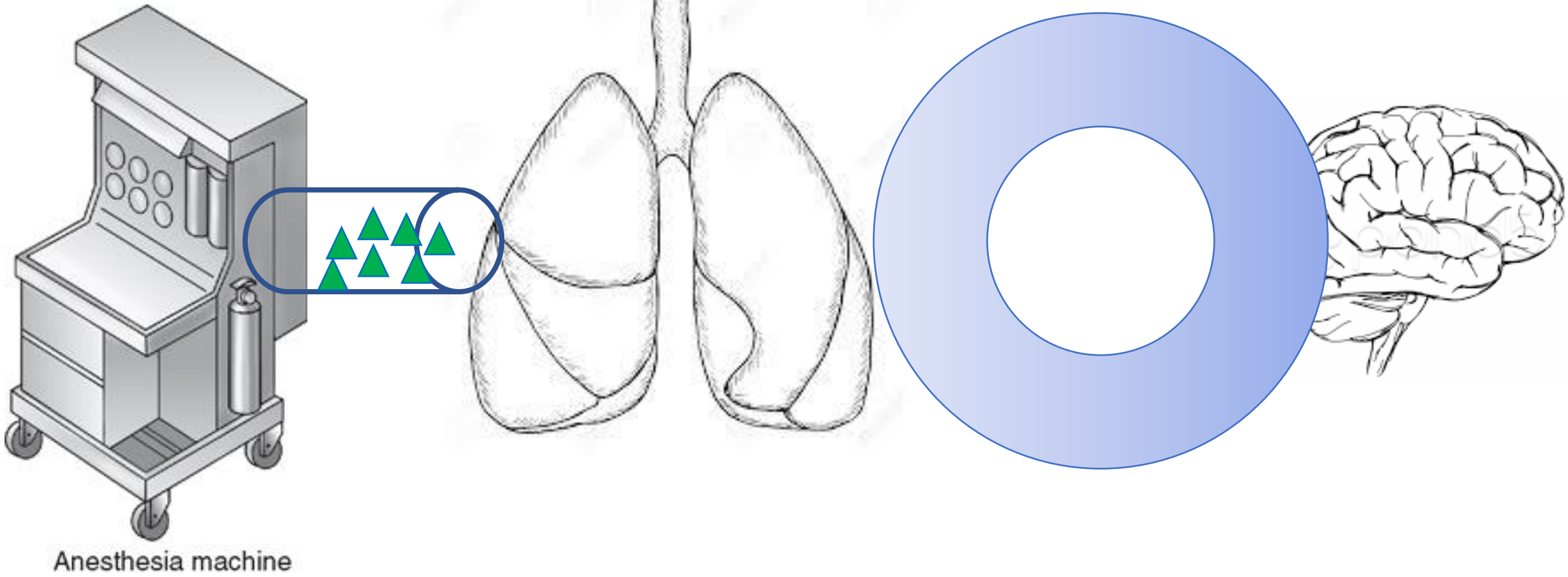
a. Solubility in blood
b. Cardiac output
c. Tissue type
d. Alveolar:venous gradient

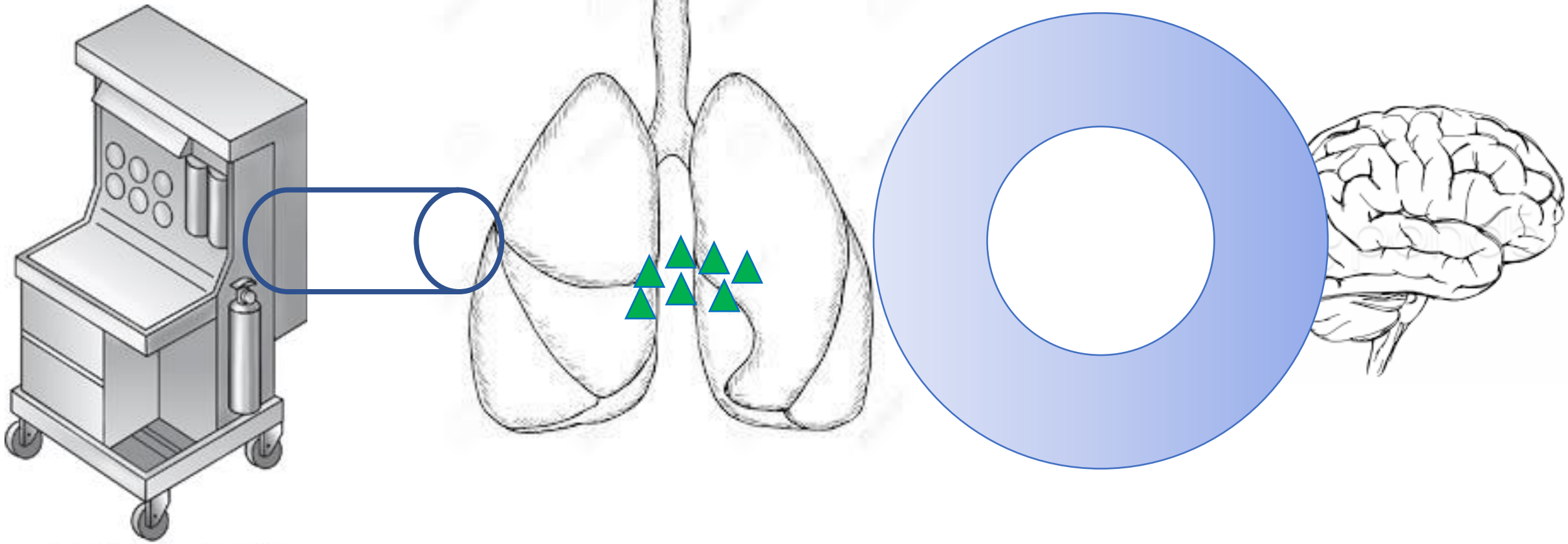
Solubility

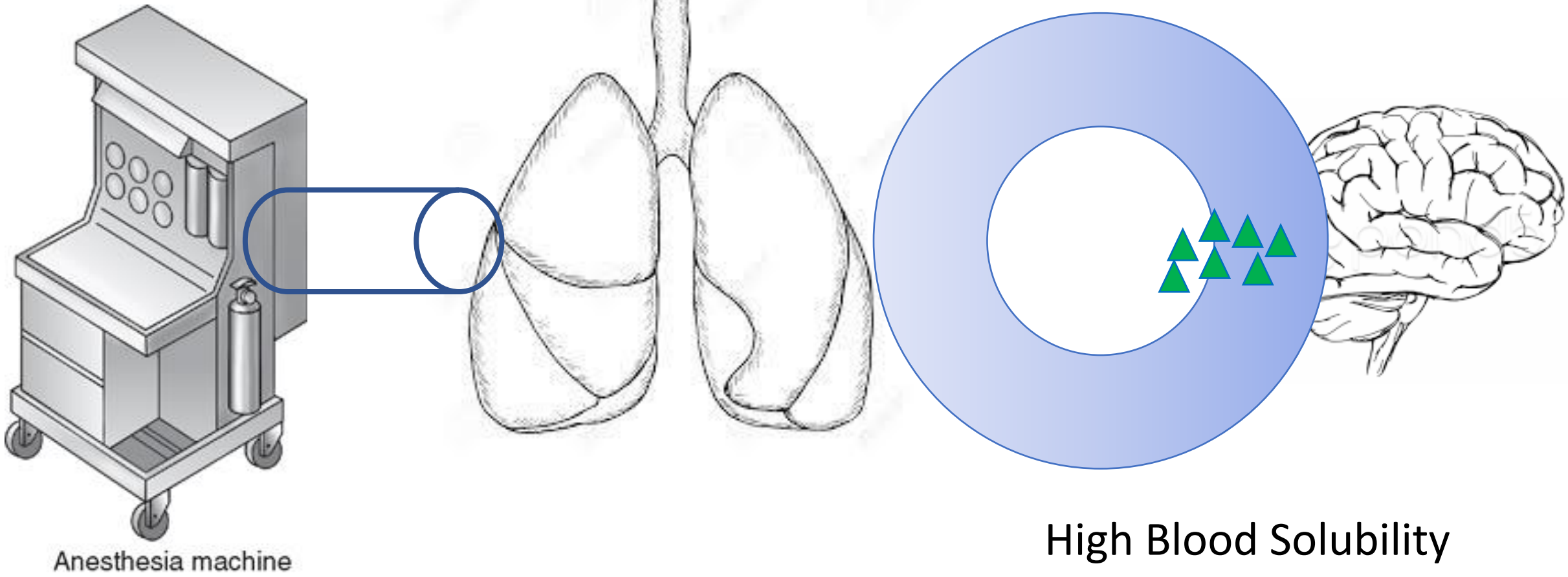
- Determined by **blood:gas partition coefficient** [the ratio of the concentration of the anesthetic in the blood to the concentration of the anesthetic in the gas phase=solubility of an anesthetic in blood]

- **Low** blood solubility → **few** anesthetic molecules are required to raise [P_a] → **Less** time for induction and recovery

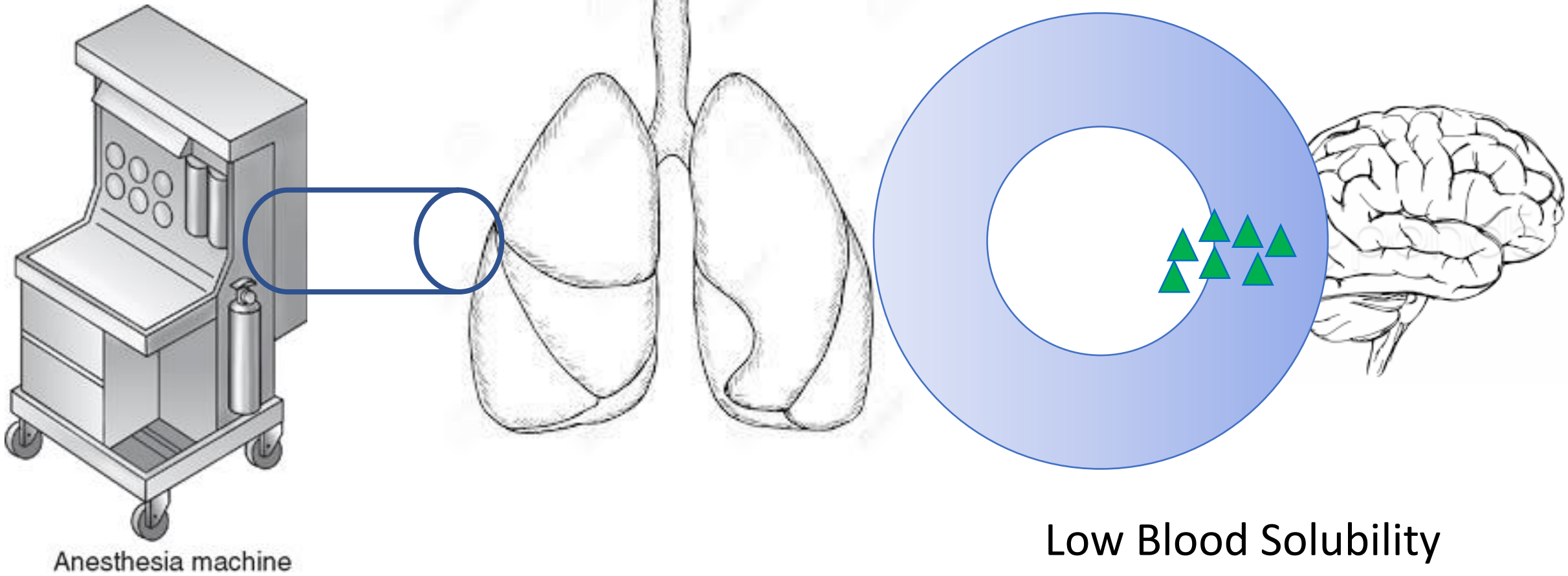
- **High** blood solubility → **more** anesthetic molecules are required to raise [P_a] → **more** time for induction and recovery



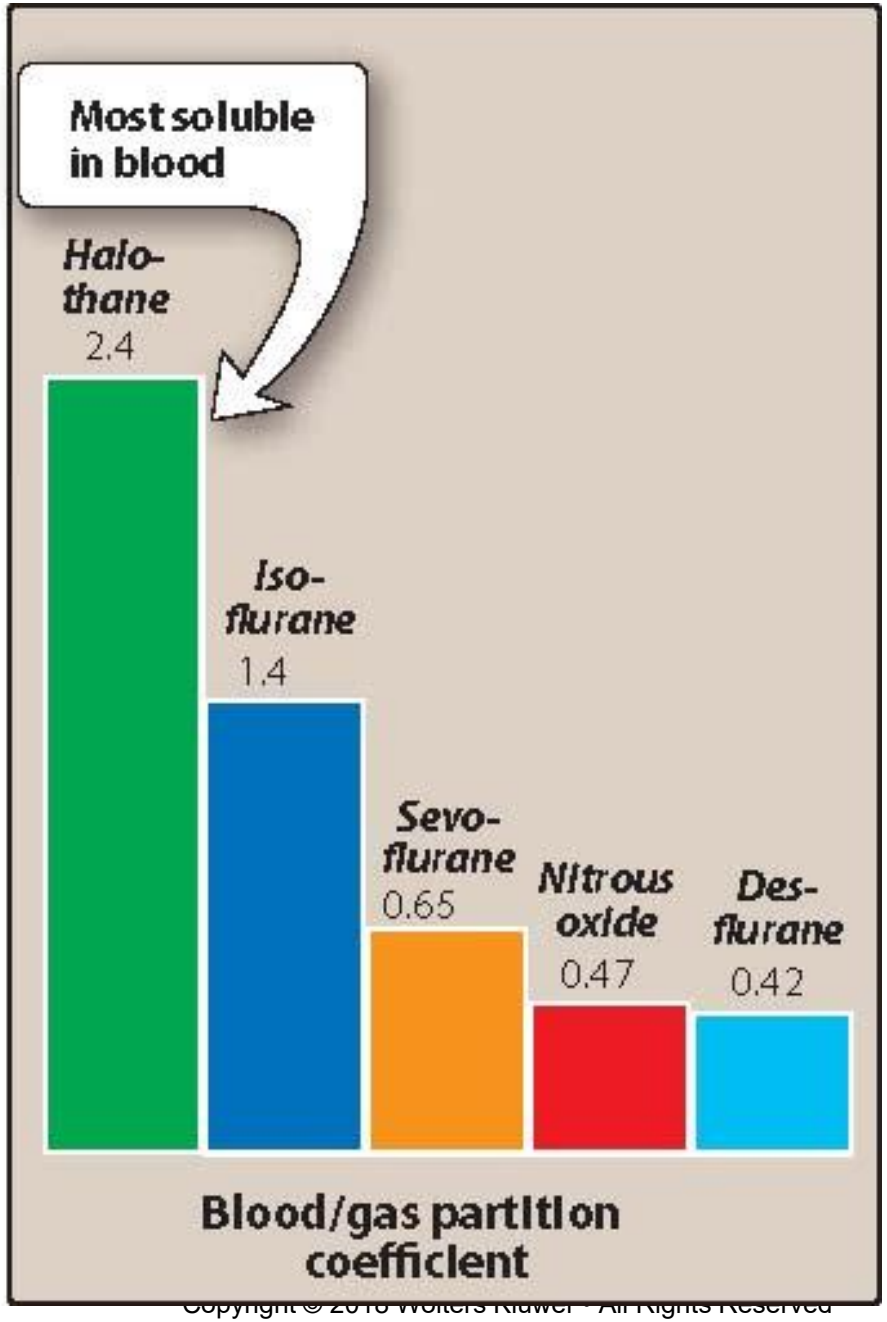




High Blood Solubility



Low Blood Solubility



Cardiac Output

- CO affects washing the anesthetic to peripheral tissue (NOT the site of action)

High CO → he periphery) → **slow** ris

COMPARE TO IV ANESTHETICS?

Low CO → ↓ pulmonary blood flow (less removal to the periphery) → **fast** rise in [P_{alv}] → **faster** induction

Differences in Tissue Type on Uptake

$$\text{Steady State} \sim \frac{\text{Blood flow to the tissue}}{\text{Capacity of tissue to store the anesthetic (proportional to tissue volume)}}$$

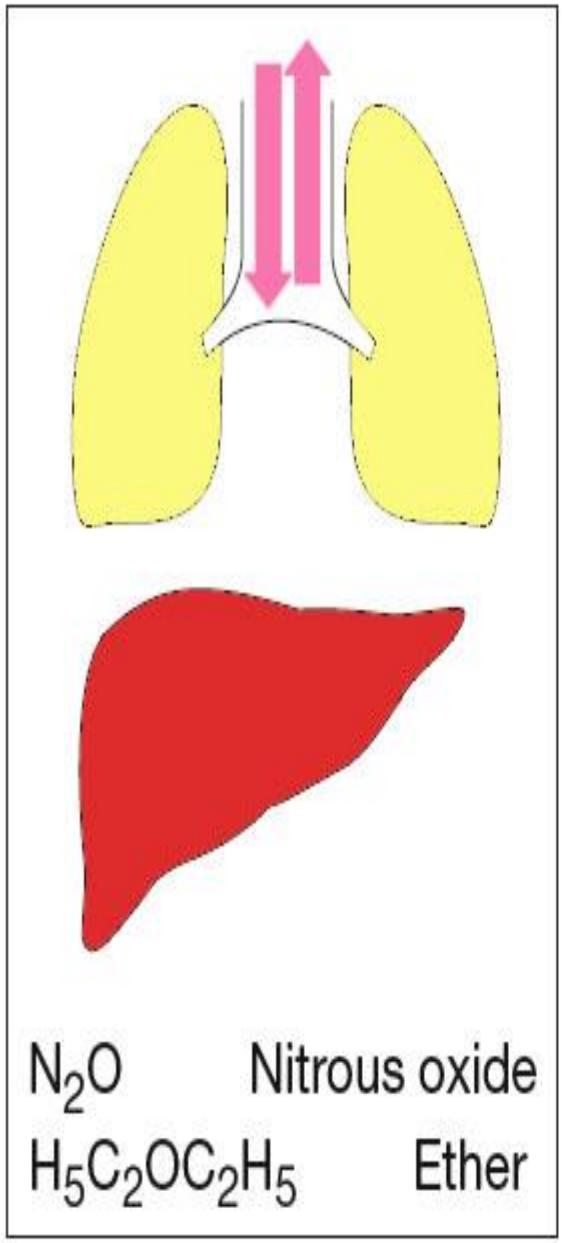
Tissue Type	Perfusion (Blood Flow)	Capacity
Brain, heart, liver , kidney, endocrine glands	Good	Low
Skeletal muscles	Poor	Large
Adipose tissue	Poor	Large
Bone, cartilage	Poor	Low

Elimination

- The time to recovery from inhalation anesthesia depends on the rate of elimination of anesthetics from the brain after the inspired concentration of anesthetic has been decreased.

- Inhaled anesthetics that are relatively insoluble in blood (low blood: gas partition coefficient) and brain are eliminated at faster rates than more soluble anesthetics.

All inhaled anesthetics are eliminated mainly through lungs

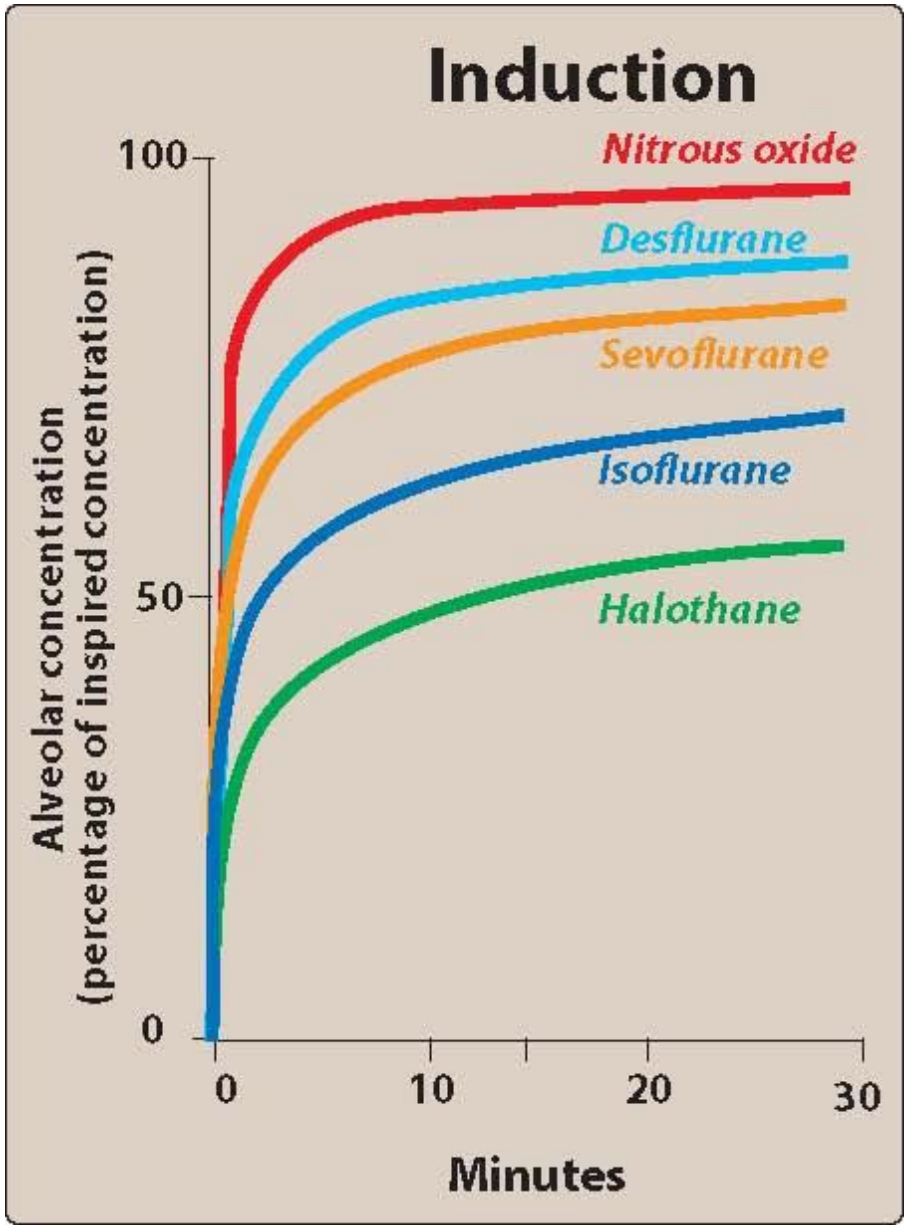


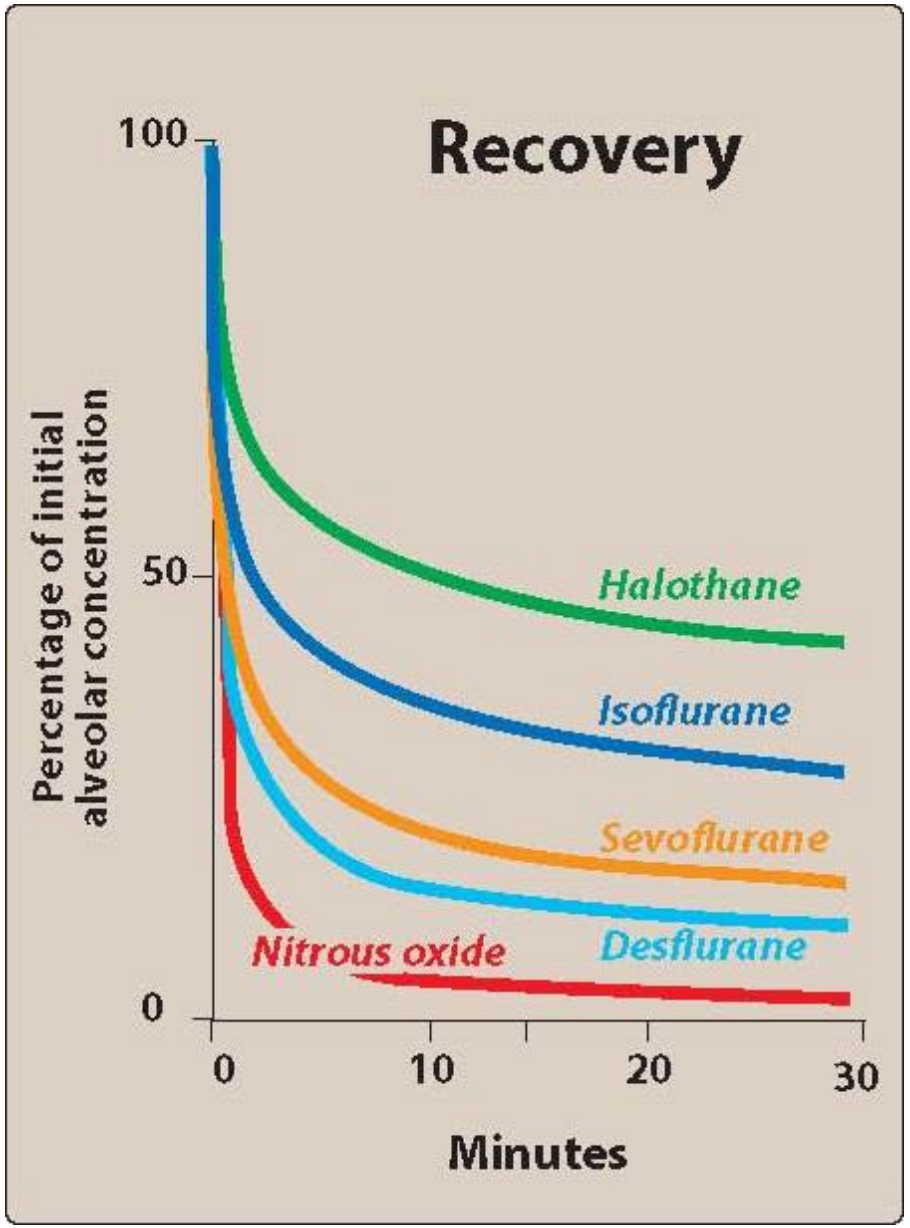
Elimination routes of different volatile anesthetics

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

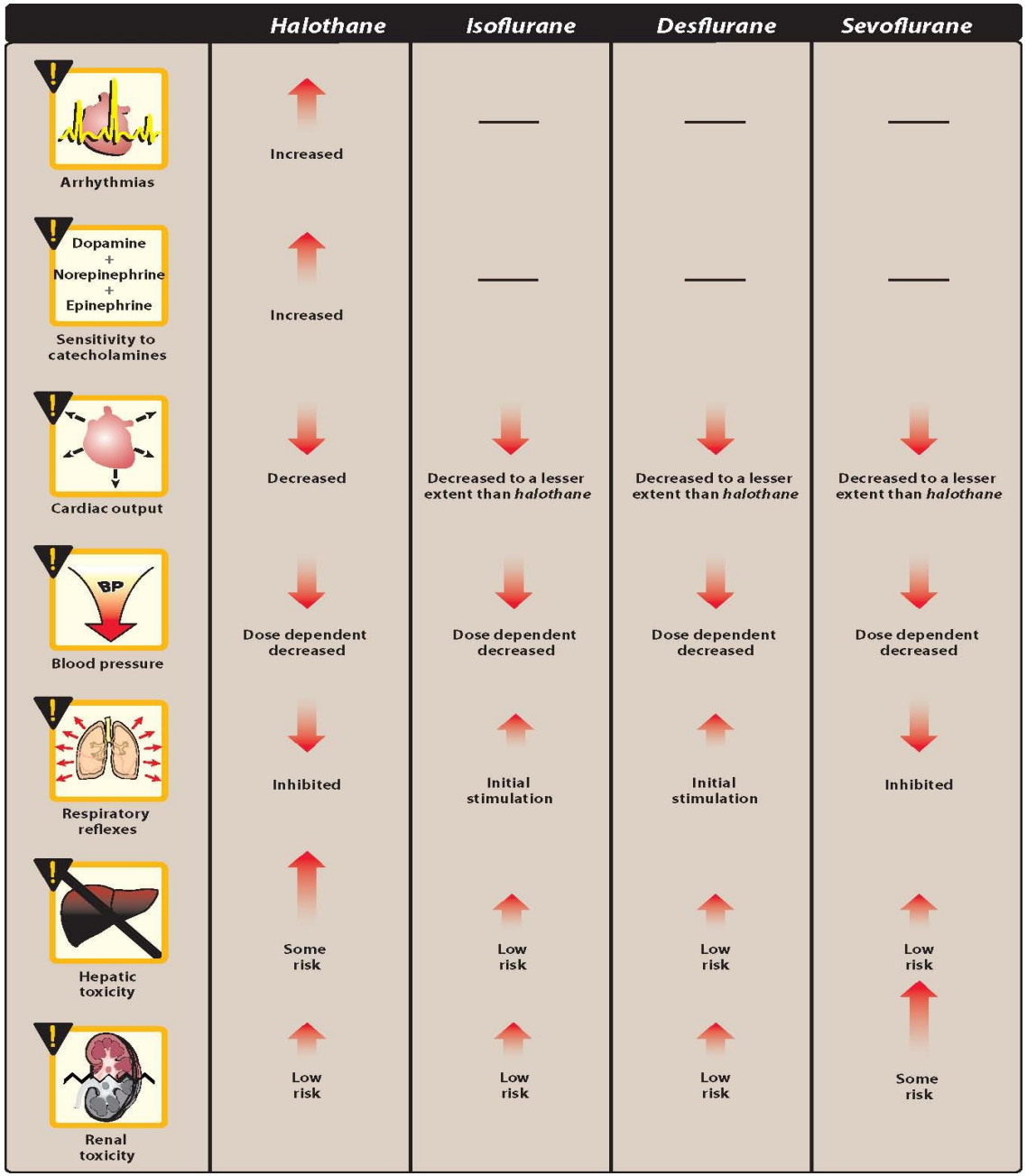
Sevoflurane

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

Nitrous Oxide

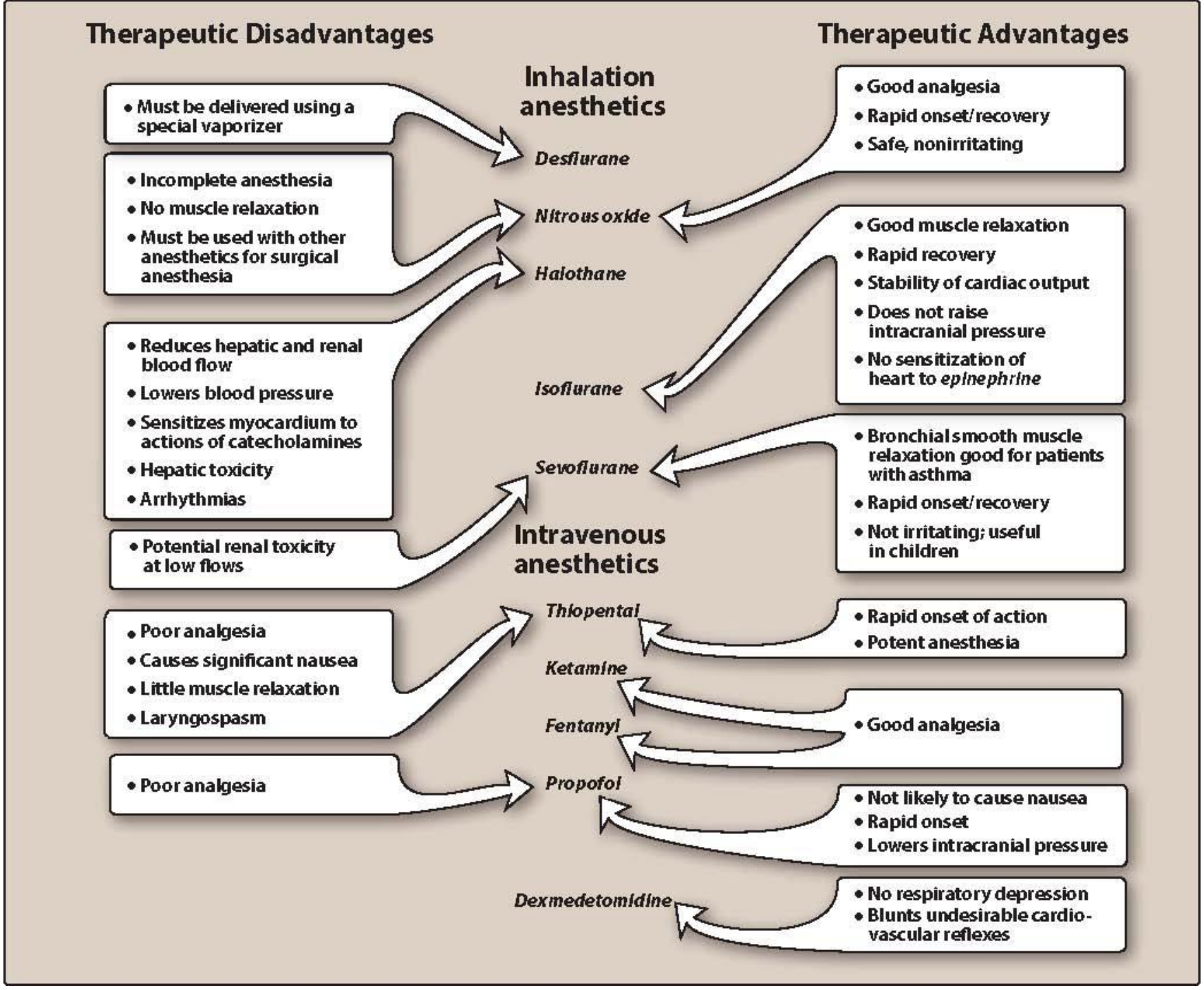
Nitrous Oxide

- Gas
- Very rapid induction and recovery.
  - Why?
- least potent, highest MAC value.
- Poor anesthetic, good analgesic
- 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



Anesthetic Adjuncts

Anesthetics Adjuncts

Anxiolytics
- Benzodiazepines

-midazolam

Facilitation of intubation
- Neuromuscular blocking agents

Anticholinergics
- WHY?

↓ gastric acid secretion
- H_2 antagonists

-famotidine

-ranitidine

Prevent allergic reactions
- antihistamines

-diphenhydramine

Antiemetics
- ondansetron

Analgesics
- NSAIDS
- Paracetamol
- Opioids (fentanyl)

Stages of Anesthesia

INDUCTION

- Mostly using intravenous anesthetics

  -*propofol*

- Produce unconsciousness in 30-40 seconds
- Could use an inhalational agent e.g., pediatric

MAINTENANCE

- Mostly using inhalational agents
- Combined with fentanyl to produce analgesia

RECOVERY

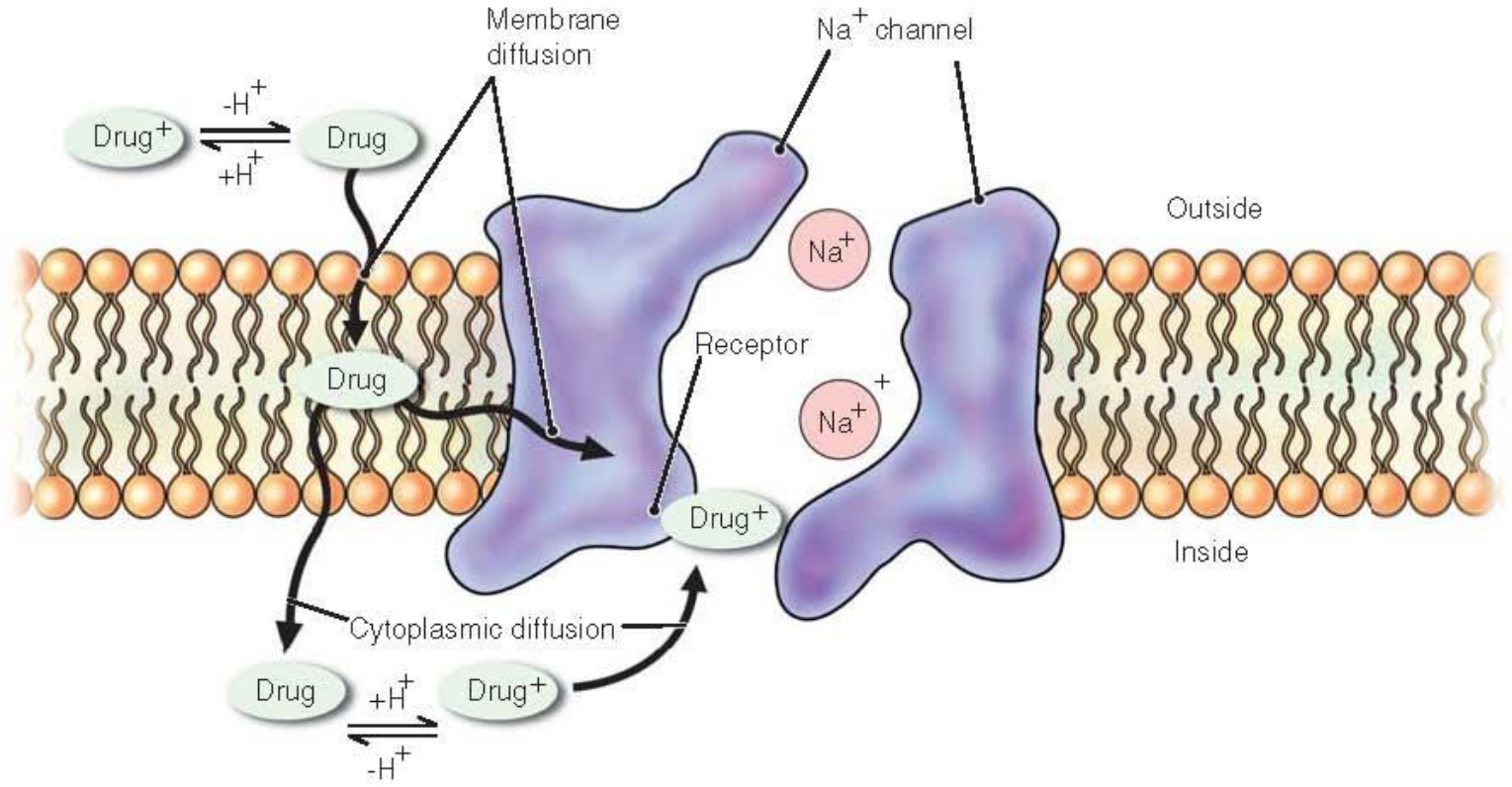
- Recovery happens due to the **redistribution** rather than metabolism

Local Anesthetics

Local Anesthetics

- Low doses: block sensory conduction
- High doses: block motor impulses

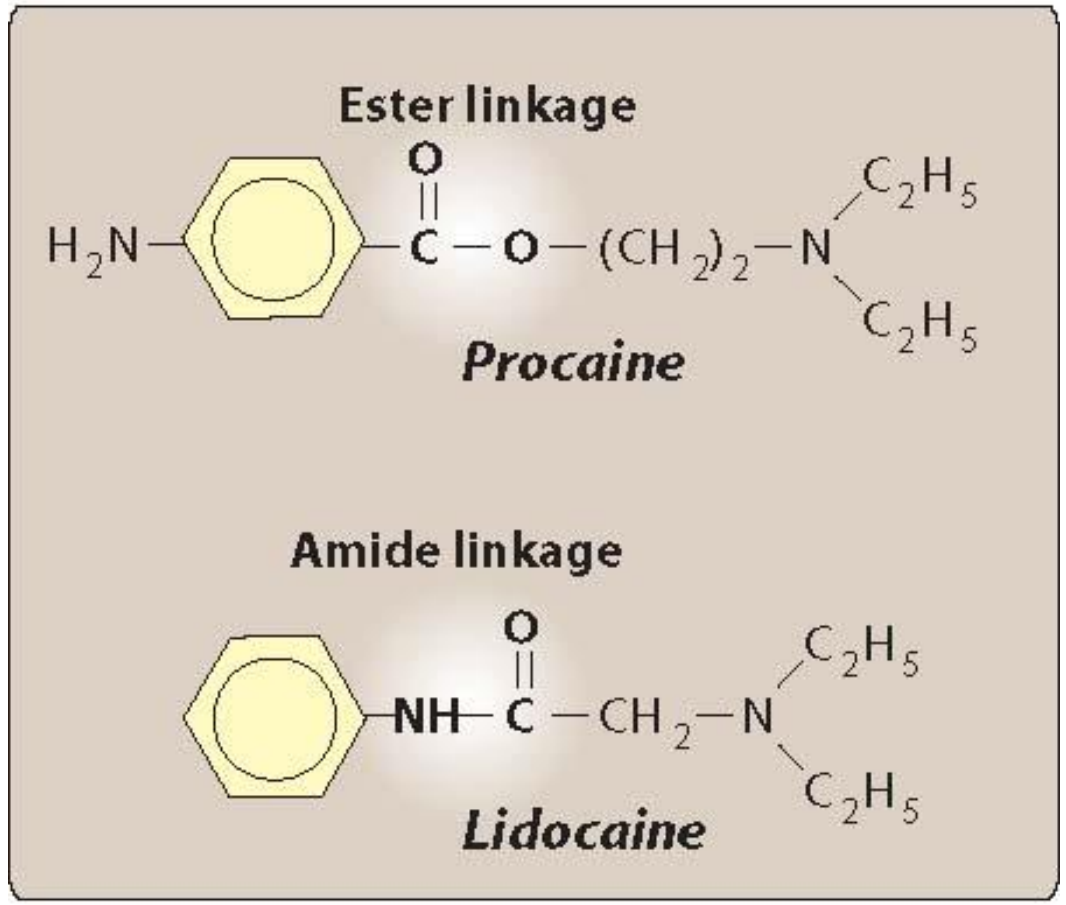
- **Mechanism of action:** "Sodium channels blockade"



GAs appear to act by depressing synaptic transmission (unlike local anesthetics which act primarily by blocking axonal conduction)

Delivery Options

- Topical
- Infiltration
- Perineural
- Neuraxial
  - Spinal
  - Epidural
  - Caudal



LOCAL ANESTHETICS: AMIDES

Bupivacaine MARCAINE
Lidocaine XYLOCAINE
Mepivacaine CARBOCAINE
Ropivacaine NAROPIN

LOCAL ANESTHETICS: ESTERS

Chloroprocaine NESACAINE
Procaine NOVOCAINE
Tetracaine PONTOCAINE

Local Anesthetics

Actions:

- **Vasodilation**
  - leads to rapid diffusion → short duration of action
  - overcome by adding a vasoconstrictor e.g., *epinephrine*

- **Antiarrhythmic**
  - e.g., *lidocaine*

Local Anesthetics

Duration of actions:

- **Factors affecting the duration of action:**

1. Tissue pH
2. Nerve morphology
3. Concentration
4. Lipid solubility
5. pKa (most important)
   - lower pKa → more ionized at physiologic pH → faster
   - What happens if the tissue is infected?

Hepatic metabolism does NOT affect duration of action of local anesthetics

Systemic Toxicity

- What if a local anesthetic was administered frequently or inadvertently in the vein (IV)?

❑ Local Anesthetic Systemic Toxicity (LAST)

1. Altered mental status
2. Seizures
3. Cardiovascular instability

Treatment: Lipid Rescue Therapy (20% lipid emulsion infusion)

CHARACTERISTIC	ESTERS • *Procaine* • *Tetracaine* • *Chloroprocaine* • *Cocaine*	AMIDES • *Lidocaine* • *Mepivacaine* • *Bupivacaine* • *Prilocaine* • *Ropivacaine*
Metabolism	Rapid by plasma cholinesterase	Slow, hepatic
Systemic toxicity	Less likely	More likely
Allergic reaction	Possible- PABA derivatives form	Very rare
Stability in solution	Breaks down in ampules (heat, sun)	Very stable chemically
Onset of action	Slow as a general rule	Moderate to fast
pK_a's	Higher than physiologic pH (8.5–8.9)	Close to physiologic pH (7.6–8.1)

DRUG	POTENCY	ONSET	DURATION
Procaine	Low	Rapid	Short
Chloroprocaine	Low	Rapid	Short
Tetracaine	High	Slow	Long (spinal)
Lidocaine	Low	Rapid	Intermediate
Mepivacaine	Low	Moderate	Intermediate
Bupivacaine	High	Slow	Long
Ropivacaine	High	Moderate	Long

- Thank you
- Questions?