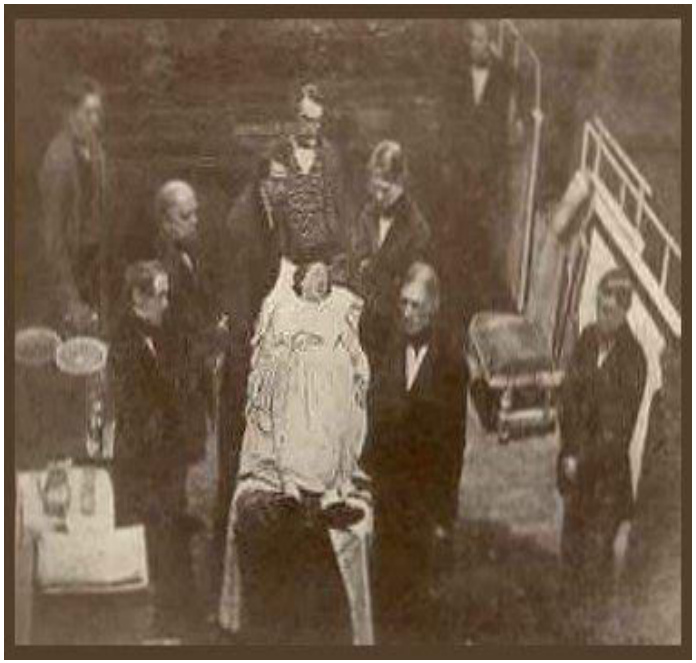
General Anesthetics

What are General Anesthetics?

- A drug that brings about a reversible loss of consciousness.
- These drugs are generally administered by an anesthesiologist in order to induce or maintain general anesthesia to facilitate surgery.

Background

- **General anesthesia was absent until the mid-1800's**
- **William Morton** administered ether to a patient having a neck tumor removed at the Massachusetts General Hospital, Boston, in October 1846.
- The discovery of the **diethyl ether** as general anesthesia was the result of a search for means of eliminating a patient's pain perception and responses to painful stimuli.



$(CH_3CH_2)_2O$

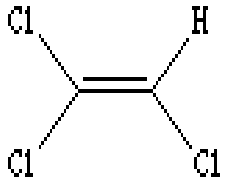
Anesthetics divide into 2 classes:

- **Inhalation** Anesthetics
  - Gasses or Vapors
  - Usually Halogenated
- **Intravenous** Anesthetics
  - Injections
  - Anesthetics or induction agents

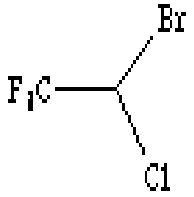
Inhaled Anesthetics

- Halothane
- Enflurane
- Isoflurane
- Desflurane

ethyl chloride

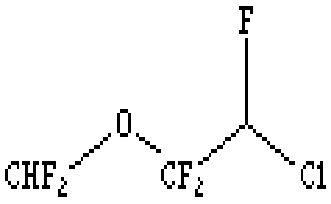


trichloroethylene

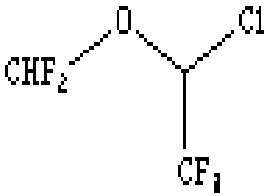


halothane, U.S.P.
(Fluothane®)

methoxyflurane, U.S.P.
(Penthrane®)



enflurane, U.S.P.
(Enthrane®)

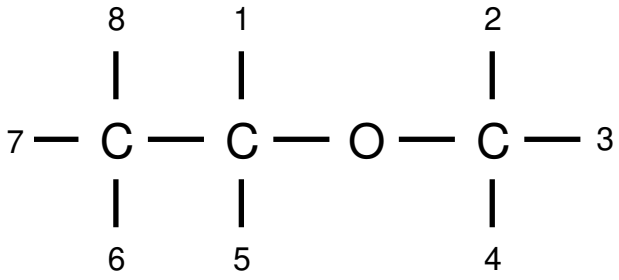


isoflurane
(Forane®)

Physical and Chemical Properties of Inhaled Anesthetics

- Although halogenations of hydrocarbons and ethers increase anesthetic potency, it also increase the potential for inducing cardiac arrhythmias in the following order F<Cl<Br.1
- Ethers that have an asymmetric halogenated carbon tend to be good anesthetics (such as Enflurane).

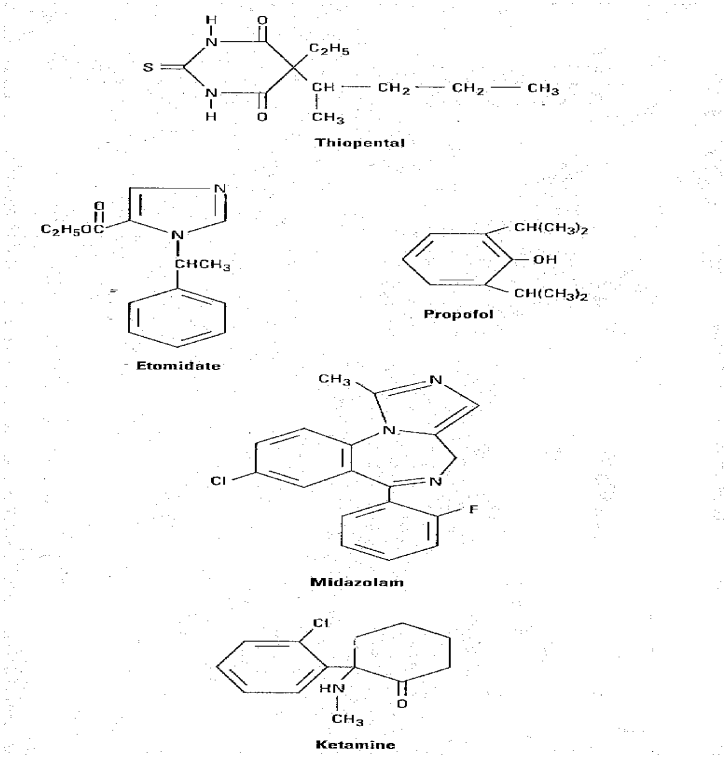
Overview



	MW	1	2	3	4	5	6	7	8
Diethyl ether	74	H	H	CH_3	H	H	H	H	H
Fluroxene	126	H	H	$=CH_2$		H	F	F	F
Methoxyflurane	165	F	H	H	H	F	Cl	H	Cl
Desflurane	168	H	F	H	F	F	F	F	F
Isoflurane	184	H	F	H	F	Cl	F	F	F
Enflurane	184	F	F	H	F	F	Cl	H	F
Sevoflurane	200	H	H	F	H	CF_3	F	F	F

Intravenous Anesthetics

- Used in combination with Inhaled anesthetics to:
  - Supplement general anesthesia
  - Maintain general anesthesia
  - Provide sedation
  - Control blood pressure
  - Protect the brain



Essential Components of Anesthesia

- Analgesia- perception of pain eliminated
- Hypnosis- unconsciousness
- Depression of spinal motor reflexes
- Muscle relation

* These terms together emphasize the role of immobility and of insensibility!

Hypotheses of General Anesthesia

1. Lipid Theory: based on the fact that anesthetic action is correlated with the oil/gas coefficients.
   - The higher the solubility of anesthetics is in oil, the greater is the anesthetic potency.
   - Meyer and Overton Correlations
   - Irrelevant

2. Protein (Receptor) Theory: based on the fact that anesthetic potency is correlated with the ability of anesthetics to inhibit enzymes activity of a pure, soluble protein. Also, attempts to explain the $GABA_A$ receptor is a potential target of anesthetics acton.

Other Theories included

- Binding theory:
  - Anesthetics bind to hydrophobic portion of the ion channel

Mechanism of Action

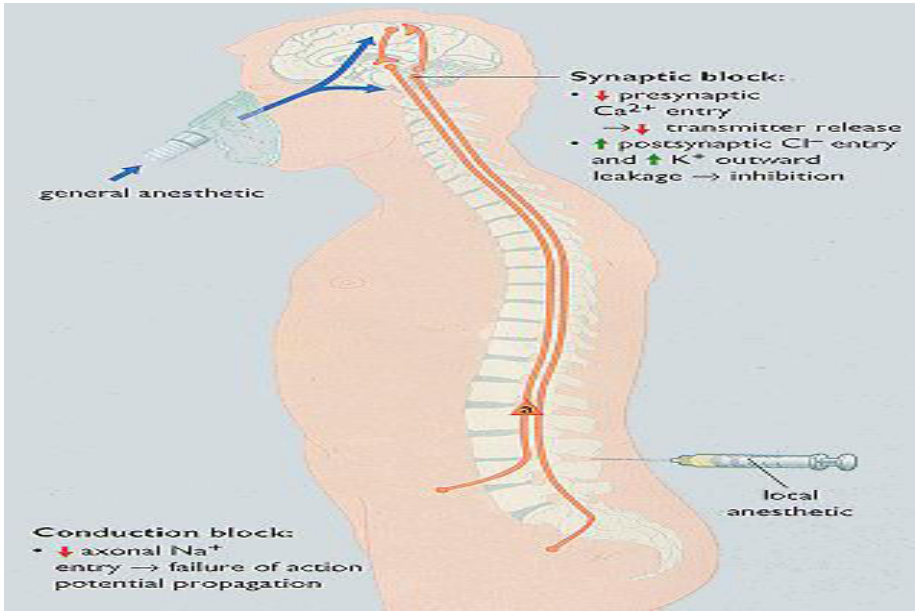
UNKNOWN!!

- Most Recent Studies:
  - General Anesthetics acts on the CNS by modifying the electrical activity of neurons at a molecular level by modifying functions of ION CHANNELS.
  - This may occur by anesthetic molecules binding directly to ion channels or by their disrupting the functions of molecules that maintain ion channels.

Cont on Mechanism

- Scientists have cloned forms of receptors in the past decades, adding greatly to knowledge of the proteins involved in neuronal excitability. These include:
  - Voltage-gated ion channels, such as sodium, potassium, and calcium channels
  - Ligand-gated ion channel superfamily and
  - G protein-coupled receptors superfamily.

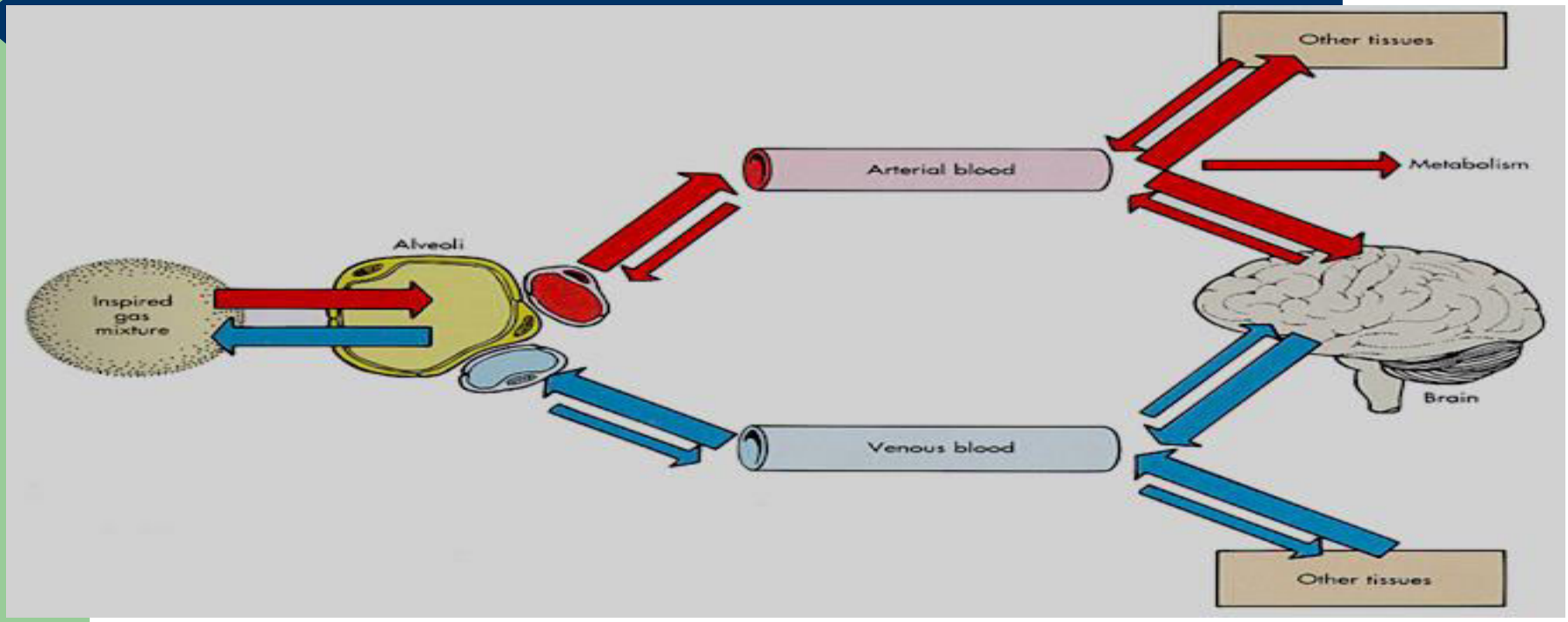
Anesthetic Suppression of Physiological Response to Surgery



Pharmacokinetics of Inhaled Anesthetics

1. Amount that reaches the brain
    1. Indicated by oil:gas ratio (lipid solubility)
2. Partial Pressure of anesthetics
    1. 5% anesthetics = 38 mmHg
3. Solubility of gas into blood
    1. The lower the blood:gas ratio, the more anesthetics will arrive at the brain
4. Cardiac Output
    1. Increased CO= greater Induction time

Pathway for General Anesthetics

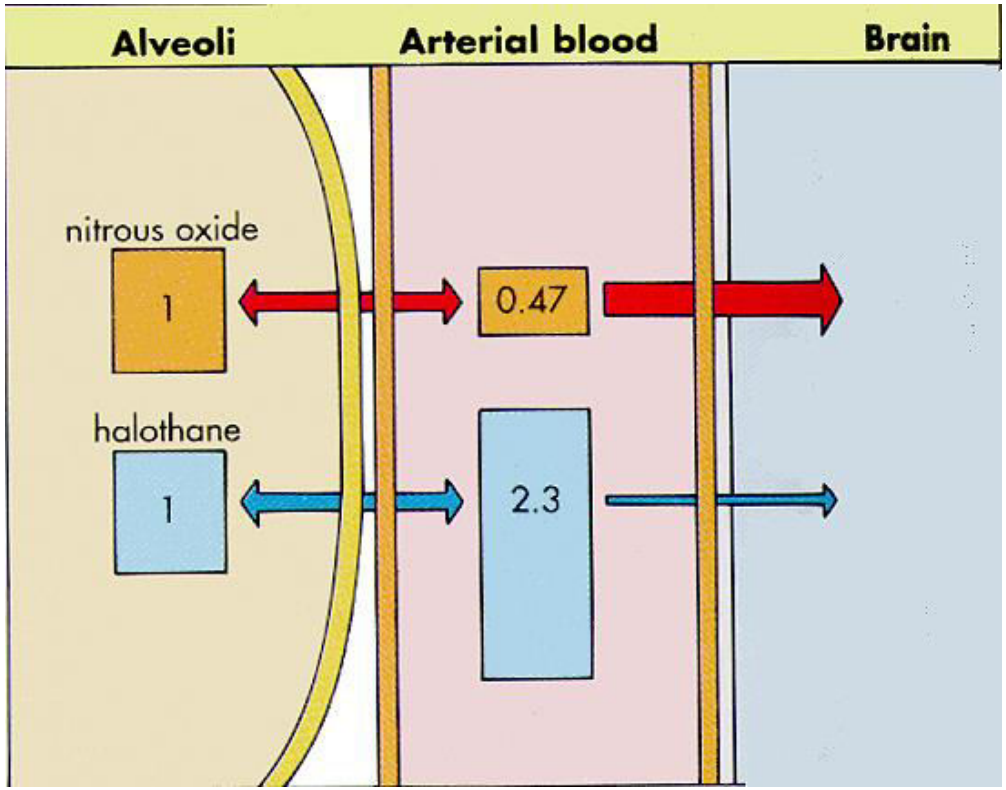


Variables that Control Partial Pressure in Brain

- Direct Physician's Control
  - Solubility of agent
  - Concentration of agent in inspired by air
  - Magnitude of alveolar ventilation

- Indirect Physician's Control
  - Pulmonary blood flow-function of CO
  - Arteriovenous concentration gradient

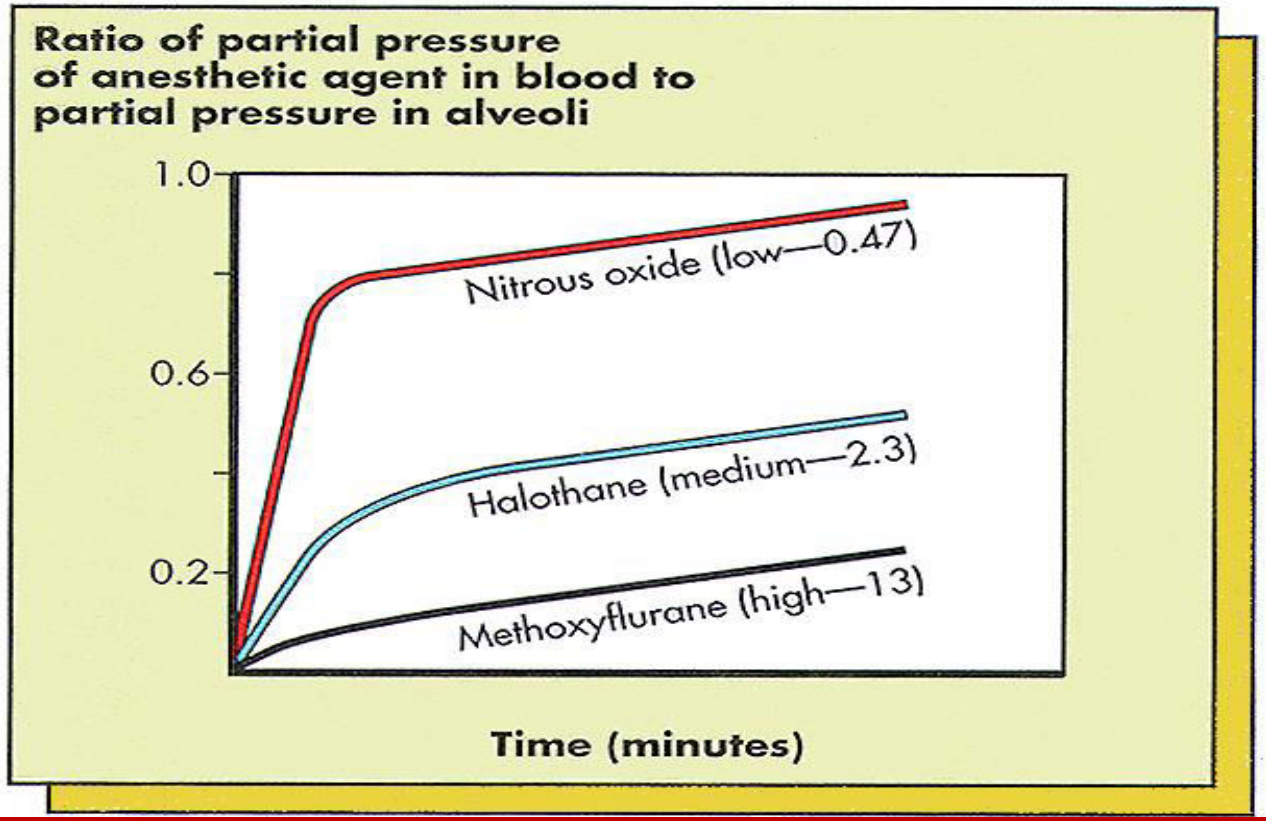
Rate of Entry into the Brain: Influence of Blood and Lipid Solubility



MAC

- A measure of potency
- 1MAC is the concentration necessary to prevent responding in 50% of population.
- Values of MAC are additive:
  - Avoid cardiovascular depressive concentration of potent agents.

Increase in Anesthetic Partial Pressure in Blood is Related to its Solubility



General Actions of Inhaled Anesthetics

- Respiration
  - Depressed respiration and response to CO_2
- Kidney
  - Depression of renal blood flow and urine output
- Muscle
  - High enough concentrations will relax skeletal muscle

Cont'

- Cardiovascular System
  - Generalized reduction in arterial pressure and peripheral vascular resistance. Isoflurane maintains CO and coronary function better than other agents
- Central Nervous System
  - Increased cerebral blood flow and decreased cerebral metabolism

Toxicity and Side Effects

- Depression of respiratory drive
  - Decreased CO2 drive (medullary chemoreceptors), Takes MORE CO2 to stimulate respiration
- Depressed cardiovascular drive
- Gaseous space enlargement by NO
- Fluoride-ion toxicity from methoxyflurane
  - Metabolized in liver = release of Fluoride ions
    - Decreased renal function allows fluoride to accumulate = nephrotoxicity

Toxicity and Side Effects

- Malignant hyperthermia
  - Rapidly cool the individual and administer Dantrolene to block S.R. release of Calcium

Refrences

- https://accesspharmacy.mhmedical.com/content.aspx?bookid=1568&sectionid=95702505
- https://www.ncbi.nlm.nih.gov/books/NBK493199/