GENERAL ANESTHESIA
INHALATION / INTRAVENOUS DRUGS

May 6, 2011

OBJECTIVES

1. Introduce the concepts of general / balanced anesthesia used during surgery.
2. Overview mechanisms of general anesthesia at a systems and cellular level.
3. Introduce drug classes combined to achieve inhalation / balanced general anesthesia.
4. Define inhalation anesthetic potency based on minimum alveolar concentration (MAC).
5. Consider pharmacokinetic principles of inhalation anesthesia induction, maintenance and recovery.
6. Discuss significant side effects / adverse events possible with inhaled agents.
7. Understand pharmacokinetic influences on action of intravenous general anesthetics.
8. Define intravenous general anesthetic drug classes and prototypical agents.

General Anesthesia is a state characterized by **fully reversible drug-induced** complete loss of consciousness, awareness of pain and immediate memory.

Balanced Anesthesia is the clinical practice of combining a wide range of drugs to improve muscle relaxation, suppress of undesirable reflexes, reduce anxiety and cause amnesia of psychologically adverse events with the purpose of improving the overall clinical outcome during general anesthesia.

Clinical Signs with Diethyl Ether-Induced General Anesthesia

The stages listed below reflect changes in physiology paralleling increasing depth of anesthesia with diethyl ether inhalation alone. This protocol introduced in 1920 provided the 1st standardized clinical protocol for induction of general anesthesia and significantly improved safety / efficacy.

I **Stage of Analgesia** (voluntary excitation / euphoria) awake to loss of consciousness - normal ocular reflexes, muscle tone, respiration

II **Stage of Excitation** (involuntary excitation) excitement, increased muscle tone just after loss of consciousness – some blunting of ocular reflexes, irregular respiration

III **Stage of Surgical Anesthesia** (planes 1-4) light to deep anesthesia - reduced muscle tone, increasing loss of ocular reflexes, no response to skin incision - most surgery at planes 2-3.

IV **Stage of Medullary Depression** (near death) respiratory / cardiovascular failure (overdosed).

Modern drugs /equipment such as intravenous agents, life support systems and supplemental drugs now require more sophisticated monitoring of vital signs. Respiratory rate, body temperature, PO_2, heart rate, EKG, blood pressure, response to incision, EEG (bispectral index BIS) and end tidal anesthetic gas (ETAG) concentration are used to help establish / maintain level of general anesthesia [see sup. reading: Avidan et al., NEJM 358:1097-1108, 2008].

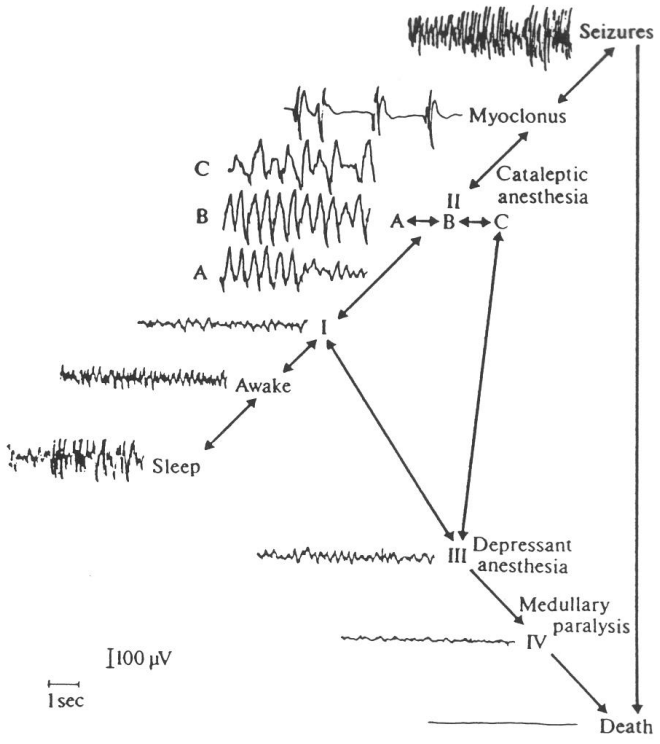
General Anesthesia Occurs In the CNS!

Primary targets include **cerebral cortex** (controls perception / association) and **reticulothalamic system** (controls alertness). Act together to produce / maintain consciousness.

A simplified view suggests unconsciousness is produced in two ways by general anesthetics acting on these structures.

Depressant General Anesthesia (ie., halothane, thiopental, propofol) - both cortex and reticulothalamic system are depressed causing loss of consciousness (see stages III & IV).

Dissociative General Anesthesia (ie., ketamine or fentanyl + droperidol) - reticulothalamic system becomes hyperactive / desynchronized preventing meaningful processing of sensory and alerting inputs to cerebral cortex, (see stage II or cataleptic stage).

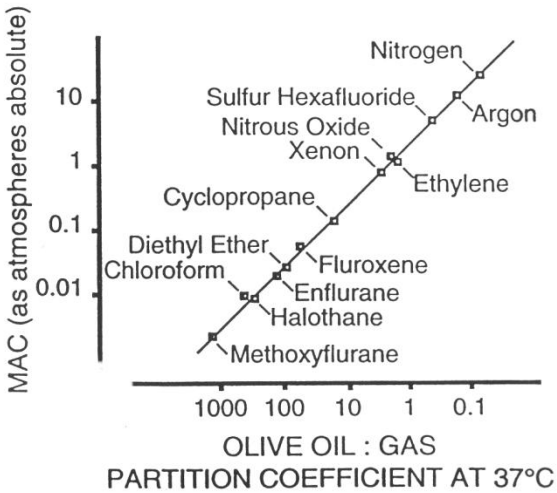


Patterns of cortical EEG activity show increases or decreases in wave height and frequency across stages I – IV of diethyl ether general anesthesia.

Cellular / Molecular Sites of General Anesthetic Action

Neurochemical transmission at the synapse is more sensitive to clinically relevant drug concentrations than axonal conduction or neuronal generation of action potentials (ie., Na^+, Ca^{2+} or K^+ voltage-gated channels). **Neurotransmitter receptors** including G protein-coupled or ligand-gated ion channels are thought to be the most likely targets! Anesthesia related actions of opioids are mediated by specific binding to Mu (μ) type opioid receptors.

Until recently, inhalation agents and many intravenous agents were not thought to have such specific receptor / binding sites. Two major competing hypotheses attempt to explain how neurotransmitter receptors are impacted by these less specific drugs (see below).



Anesthetic potency increases (ie., smaller MAC number) for agents with higher olive oil : gas coefficient (larger number) partitioning.

Membrane hypothesis or "Meyer-Overton" hypothesis originated around 1905 from observations that anesthetic potency increases directly with lipid solubility (ie., olive oil : gas partition coefficient) of the anesthetic (lipid solubility / anesthetic potency (MAC) highly correlated). It suggests that insertion of general anesthetic molecules into membrane lipids causes expansion-fluidization (Seeman hypothesis ~ 1970s) of the membrane to disrupt neurotransmitter related protein functioning. While membrane fluidization has been shown to occur it now seems unlikely to cause anesthesia [based on evidence such as the observation that increases in body temperature with a fever fluidize membranes like general anesthetics, but do not cause general anesthesia].

Protein hypothesis is now considered the most likely molecular action leading to anesthesia. Here general anesthetics act by binding directly to specific neurotransmitter receptors-ion channels in hydrophobic pockets within the folds of these functional proteins. [Example of binding pocket specificity is + / - isoflurane stereoisomers - have identical "membrane lipid interactions" but different mirror image shapes causing unequal change in protein target activity].

Specific receptor targets for molecular actions of different general anesthetics include:

Positive allosteric agonists of $GABA_A$ receptors - - Barbiturates (thiopental), benzodiazepines (midazolam), propofol, etomidate and inhaled agents (isoflurane) indirectly increase GABA activity [see *Frye, Anxiolytics, ... 10-11am 5/4/11*].

Non-competitive antagonists of N-Methyl-D-Aspartate (NMDA) type glutamate receptors - - Ketamine and nitrous oxide are non-competitive inhibitors of NMDA / glutamate-gated cation channels.

Agonists of Mu (μ) type opioid peptide receptors -- Opioids (fentanyl) direct competitive receptor activation [see *Winzer-Serhan, Opioid Drugs, 11am 3/23/11*].

Drugs used for Balanced General Anesthesia

Using **combinations of drugs** reduces the dose requirement for individual inhalation / intravenous anesthetic agents to maintain surgical general anesthesia and helps achieve a safer, better tolerated clinical experience (see below). **Supplemental preanesthetic medications** are also used to lessen adverse psychological / physiological reactions including lessening secretions, reducing anxiety, blunting pain, relaxing skeletal muscle or swiftly initiating general anesthesia.

Inhalation anesthetic agents are **halogenated hydrocarbons or ethers.** Most are liquids @ room temperature in closed containers, but easily volatilize when open to the atmosphere. Exceptions are nitrous oxide is a gas, and desflurane (lowest volatility). All are non-explosive, do not support combustion (except nitrous oxide) and are non-irritating when inhaled (except desflurane).

Desflurane (Suprane®) CF_3-CHF-O-CF_2H	Enflurane (Enthrane®)CHF_2-O-CF_2CHFCl
Halothane (Fluothane®) CF_3-CHClBr	Isoflurane (Forane®) CF_3CHCl-O-CHF_2
Nitrous Oxide N_2O	Sevoflurane (Ultane®)CH_2F-O-$CH(CF_3)_2$

Temperature-controlled vaporizers produce precise gas concentrations that are administered to the patient in combination with air, O_2, and nitrous oxide in re-breathing apparatus where concentrations can be monitored and adjusted to control depth of anesthesia and support physiological requirements (more on specific agents below). [See Avidan et al., NEJM 358:1097-1108, 2008 for example of using end tidal anesthetic gas (ETAG) concentrations to help establish general anesthesia clinically].

Intravenous (parenteral) anesthetic agents include a range of agents such as benzodiazepines (midazolam), barbiturates (sodium thiopental), etomidate, propofol and opioids (fentanyl) that can be given by **intravenous bolus injection** or **continuous low level infusion** to maintain general anesthesia after the initial induction (more specifics below).

Preanesthetics / Supplements Improving Balanced Anesthesia

benzodiazepines (diazepam) to reduce anxiety, and /or i.v. (midazolam) to aid general anesthesia induction and for amnesia to prevent disturbing memories [*see Frye, Anxiolytics, ... 10&11am 5/4/11*]

short-acting barbiturates (sodium thiopental) given i.v. to induce general anesthesia [*see Frye, Anxiolytics, ... 10&11am 5/4/11*]

opioids (morphine) for pain or (fentanyl) for i.v. to induce or maintain general anesthesia [*see Winzer-Serhan, Opioid Drugs, 11am 3/23/11*].

phenothiazines (promethazine), **butyrophenones** (droperidol) or **odansetron** block chemo-receptor trigger zone dopamine D_2 or serotonin $5HT_3$ receptors, respectively, to prevent nausea.

antimuscarinics (atropine) to induce parasympathetic blockade and reduce airway secretions, nausea and bradycardia [*see Zimmer, Cholinergic Antimuscarinics 11am 4/6/11*]

proton pump inhibitors (omeprazole)**, histamine (H_2) blockers** (famotidine) or **antacids** to reduce gastric acid or **metoclopramide** to increase gastric emptying to lower risk of aspirating gastric acid which damages the lungs.

nicotinic blockade with depolarizing (succinylcholine) and non-depolarizing (pancuronium) agents improves skeletal muscle relaxation [*see Zimmer, Cholinergic Neuromuscular Blockers 1pm 4/6/11*]

nitrous oxide usually added for its analgesic actions as well as partial general anesthetic action / pharmacokinetic-biophysical advantages (see below).

Inhalation Anesthetic Agent Potency

"Minimum Alveolar Concentration" (MAC) is the partial pressure or tension or concentration (%) of anesthetic gas in alveoli at equilibrium and 1 atmosphere pressure which allows surgical incision (or painful stimulation) in 50% of patients without evoking a reflex movement.

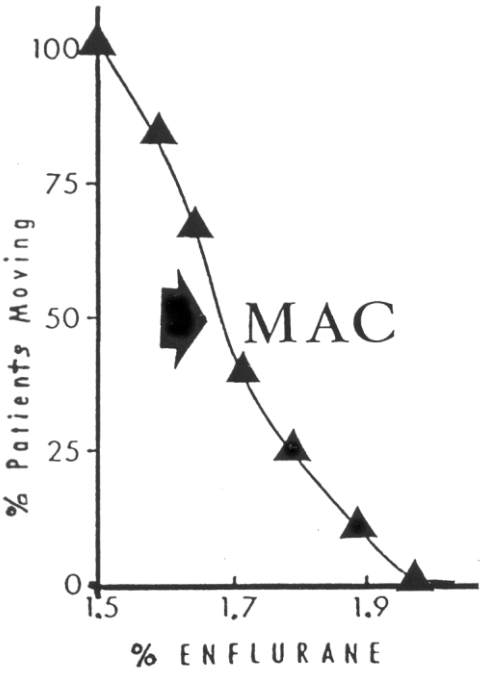
MAC measures the ED_{50} or potency of inhalation anesthetics -- unique for each drug - - a physical property of the agent.

Surgery is typically done at ~130% MAC so all patients are unconscious instead of only 50%. Supplemental CNS depressants (benzodiazepines, barbiturates, opioids, etc) reduce MAC requirements of an inhalation drug [see sup. reading: Avidan et al., NEJM 358:1097-1108, 2008].

MAC values represent the concentration of the agent as a % of inhaled gas mixtures (ie., nitrous oxide MAC is greater than 100% at 1 atmosphere). Thus MAC is the % of an inhalation agent in the breathing mixture at 1 atmosphere. MAC is <u>determined in healthy subjects in the absence of other drugs at equilibrium</u>! Useful for estimating effective dose.

MAC Values For Modern Inhalation Anesthetic Agents

	(% gas inspired = to MAC)	
Methoxyflurane	**0.2**	**(Most potent)**
Halothane	0.8	
Isoflurane	1.4	
Enflurane	1.7	
Sevoflurane	2.0	
Desflurane	6.5	
Nitrous oxide	**>100**	**(Least potent)**



Initial determinations of MAC for enflurane required inhalation of drug alone and testing of a noxious stimulus simulating an incision.

MAC is generally resistant to change with the following few exceptions:

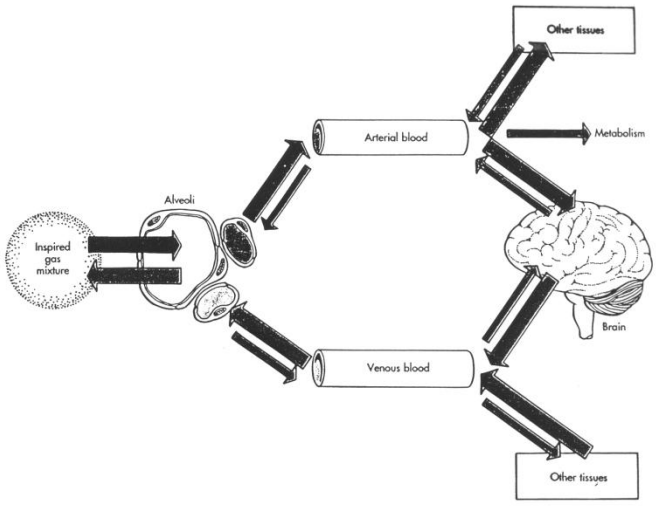
- age decreases MAC requirements
- body temperature inversely alters MAC
- theoretically, 2 inhalation anesthetics are additive (e.g. 1/2 MAC drug A + 1/2 MAC drug B = 1 MAC of either drug)
- MAC increases with CNS stimulants but decreases with CNS depressants
- Chronic sedative-hypnotic drug use induces <u>cross-tolerance</u> which increases MAC.

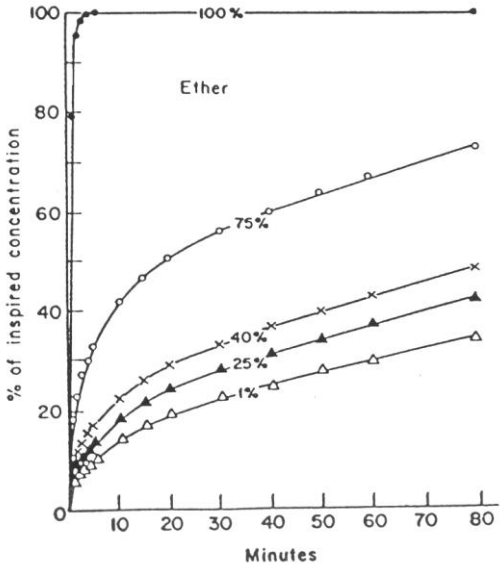
FYI > > > > > **Gas concentrations** can also be stated in other units such as **tension** (torr) or **partial pressure** (mm Hg) in addition to **concentration** (%). These units are inter-changeable and all represent the proportion of a gas in a mixture - **1 atmosphere (atm.) = 100% = 760 torr = 760 mmHg). This also applies to inhalation anesthetic agents as part of a breathing mixture.**

<u>Air</u>: Oxygen = 21% 0_2 + 79% N_2 ..... or 160 torr 0_2 + 600 torr N_2 ..... or 160 mmHg 0_2 + 600 mmHg N_2

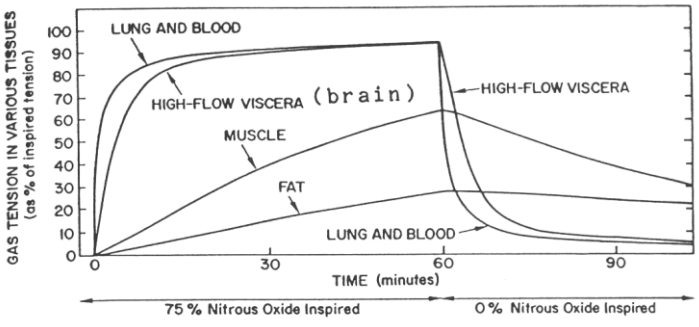
Inhalation Anesthetic Agent Pharmacokinetics

Anesthesia depends on brain gas tension! Brain tension is directly related to gas tension in the alveoli *at equilibrium* (see figures below).

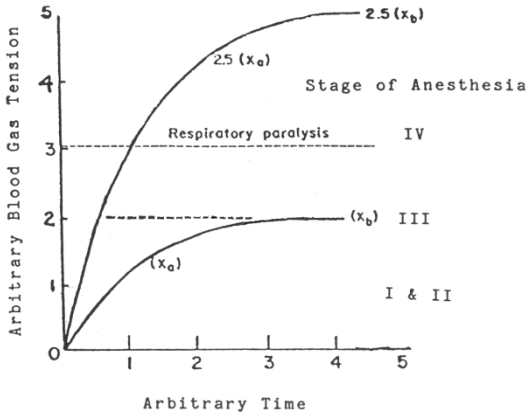




(TOP LEFT) Initially drug in the inspired gas mixture drives passive diffusion from alveoli into arterial circulation and then to tissues / brain (drugs move down a concentration gradient), but as tissue tension rises, some drug also returns to blood / alveoli. **(BELOW LEFT)** Over time, drug returning to alveoli increases toward the inspired concentration (e.g., 100%). **Equilibrium** is a *theoretical condition* where drug entering and leaving all compartments (including alveoli & brain) is the same as the inspired gas tension tension (e.g., 100%). **(TOP RIGHT)** initially adding more drug (e.g.., 75% vs 1%) to the inspired gas mix increases the early rate of diffusion into tissues to speed **induction** of general anesthesia. This is used briefly like a *"loading dose"* **(BELOW RIGHT)** to quickly achieve a brain tension of drug for surgical anesthesia (e.g., 2.5xa) before lowering the inspired partial pressure to that needed for **maintenance** of general anesthesia (e.g., xb) - [On right (I - IV) are stages of ether anesthesia (III = surgery)]. **Recovery** from anesthesia depends on loss of drug from brain **(BELOW LEFT)** which follows removal of drug from the inspired gas mix so drug diffuses out of tissues to alveoli to be exhaled.



Tissue tensions of an anesthetic gas during uptake and elimination.



Breathing higher concentrations early on speeds induction and is used as a loading dose.

Increasing respiration rate slightly speeds induction by quickly exchanging alveoli air for volatile drug vapors (mechanically or with CO_2). Increasing respiration does not change ***final equilibrium tension*** when all body compartments are saturated with drug at the inhaled level. Respiratory rate has no effect on MAC.

Rapid pulmonary blood flow delays induction slightly, if alveolar gas load is not efficiently transferred to blood, but is difficult to manipulate.

High blood flow organs like brain get drug faster and approach the inhaled drug tension sooner than low blood flow tissues like fat, but with time low blood flow organs also accumulate drug (see figure above)!

Solubility of inhalation drugs in blood can effect rate of drug diffusion / uptake, because blood acts like a sponge which soaks up and holds drug away from brain initially.

"Blood: gas partition coefficient" measures drug solubility in blood relative to gas. Called lambda (λ) and is unique for each drug.

Low solubility (affinity) for blood = small lambda so brain gas tension increases rapidly, since little drug is lost to / held in blood. Speeds induction of anesthesia and quickens recovery.

High solubility (affinity) for blood = large lambda so brain gas tension increases slowly since much drug is lost to / held in the blood. This slows induction of anesthesia and prolongs recovery.

Blood : Gas Values For Modern Inhalation Agents

Blood:Gas Partition Coefficients (λ)

Desflurane	**0.42**	**- - - - - - - - - Least blood soluble**
Nitrous oxide	0.47	
Sevoflurane	0.69	
Isoflurane	1.4	
Enflurane	1.8	
Halothane	2.3	
Methoxyflurane	**12.0**	**- - - - - - - - - Most blood soluble**

Recovery from Inhalation General Anesthesia

Depends on how fast drug leaves brain - drops below level for unconsciousness.

Conditions that slow induction also slow recovery (e.g., faster anesthetic exhalation). Drugs with **high blood solubility** show slower recovery. Also, **prolonged anesthesia** eventually saturates all body compartments (e.g. approaches equilibrium) and can slow recovery, since more drug is present in tissues and must be lost. For example, recovery from a long procedure that used highly blood soluble methoxyflurane would be much slower vs nitrous oxide or desflurane which have low blood solubility, since drug in blood and fat / muscle tissues compartments also must fall before the brain tension can fall rapidly.

Other Drug Actions that are a Concern Clinically

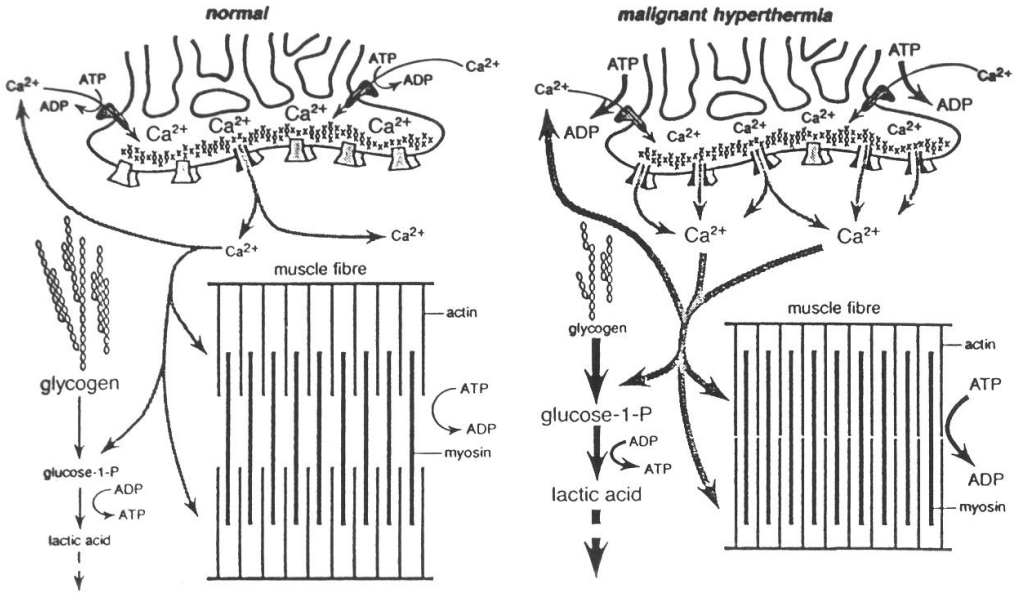
Respiratory depression occurs with all inhalation agents due to blunted medullary respiratory drive and with muscle relaxant-induced paralysis makes mechanical ventilation necessary. An advantage of inhalation agents over intravenous drugs for general anesthesia is the ability to rapidly adjust the depth of CNS depression to fine tune anesthesia and lessen other depressant side effects.

Impaired cardiovascular function = generally halothane and to a lesser extent other inhalation agents **reduce blood pressure**. This is used to monitor depth of anesthesia. Pressure falls with **reduced cardiac contractility** and **depression of SA node**. Ca^{2+} efflux from sarcoplasmic reticulum is slowed and CNS sympathetic outflow is blunted – so vagal tone also acts to slow heart rate. Muscarinic blockers (atropine) can reduce bradycardia. Adrenergics can be used to increase blood pressure, but **halothane sensitizes the heart to catecholamines** inducing arrhythmias in diseased hearts so it is contraindicated in those with cardiovascular disease.

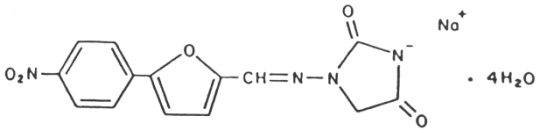
Succinylcholine interactions - often noted potential adverse events frequently associated with succinylcholine use in general anesthesia. **Muscle pain** (postoperative myalgia) lasts 2-3 days *as high as 50%*. **Hyperkalemia** from K^+ released by succinylcholine in those with tissue trauma potentially sufficient to trigger cardiac arrest. **Transient increased intraocular pressure** - contraindicated for anterior chamber procedures. **Increased intragastric pressure** - potential risk for emesis-related aspiration.

Malignant hyperthermia from sustained skeletal muscle contracture, increases body temperature, causes cardiovascular stress and is potentially lethal. **Inhalation anesthetics** and **antipsychotics** aggravate a rare mutation in sarcoplasmic reticulum Ca^{2+} release (ryanodine receptor *RYR1*) exaggerates excitation-coupling causing sustained skeletal muscle contraction and heat production (see below).

Dantrolene (Dantrium®) blocks sarcoplasmic reticulum Ca^{2+} release at the ryanodine receptor and is lifesaving by ending sustained muscle contracture!



In Malignant Hyperthermia, drugs aggravate / exaggerate Ca^{2+} release from sarcoplasmic reticulum in skeletal muscle sustaining contracture and generating life-threatening metabolic heat production. Dantrolene can block Ca^{2+} release stopping sustained contractions.



dantrolene

Nephrotoxicity with Methoxyflurane (see below) - little used due to **accumulation of fluoride ions** from metabolism ~ 60 % (* see below) - if F^- is above 40 μM can cause kidney damage.

Elimination primarily by exhalation (except for methoxyflurane)

Extent of metabolism depends on blood solubility (see below) and tissue solubility. High affinity for blood / tissues slows drug exhalation and increases exposure to liver metabolism.

Relationship between metabolism and blood solubility

Agent	Amounts excreted unchanged	Blood Solubility (λ)
methoxyflurane*	**40%**	**12.0**
halothane	80%	2.3
enflurane	90%	1.8
sevoflurane	97%	0.69
isoflurane	98%	1.4
nitrous oxide	>99%	0.47
desflurane	>99%	0.42

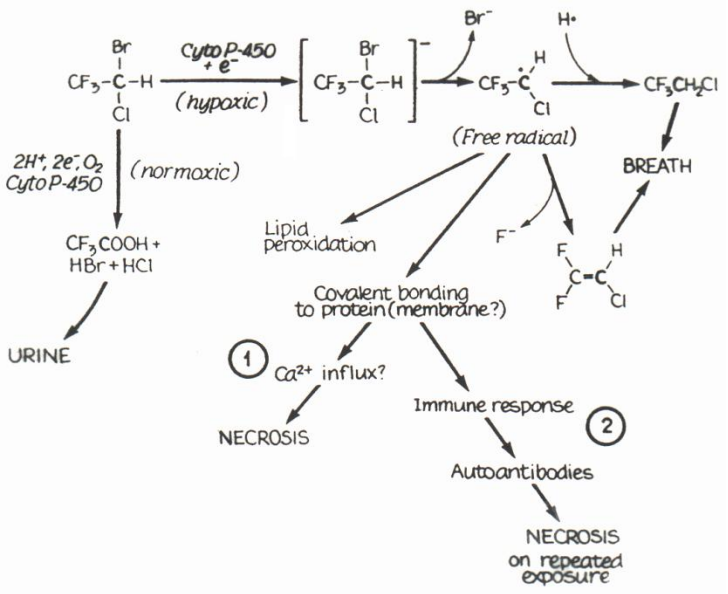
Post anesthesia hangover results from lingering actions of residual inhalation agents, their metabolites and supplemental CNS depressants on the brain. Though insufficient for general anesthesia these can still impair CNS function (e.g., intoxicate) until eliminated.

Halothane hepatitis is life-threatening liver damage which is relatively <u>rare</u> in adults (does not occur in children) after single or multiple exposures. 1st exposures = 1 case in 30,000; Multiple exposures = 1 case in 10,000; 10% of cases are lethal.

Histopathology resembles viral hepatitis. It is due to toxic halothane free radical metabolites during initial and subsequent exposures (see figure -- path 1). There is also evidence for an autoimmune reaction to free-radical bound proteins which become immunogenic (see figure -- path 2).

Free radical formation is triggered by hypoxia in liver.

Under reduced oxygen levels in the liver, cytochrome P-450 functions as a reductase producing toxic free radicals.



Metabolism of halothane under hypoxic conditions can produce free radicals that are directly toxic or can covalently bind liver proteins triggering autoimmunity.

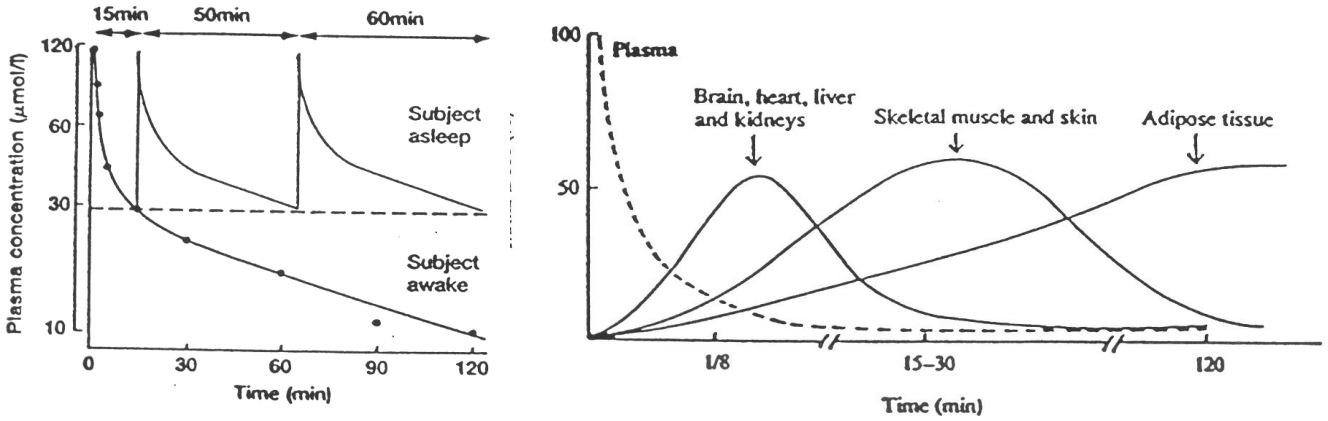
Induction / Maintenance of General Anesthesia with Intravenous Drugs

Bolus injections make it difficult to regulate anesthetic depth or reverse overdose during longer surgical procedures. However, bolus injection is regularly used to initiate **rapid smooth induction general anesthesia** before switching to inhalation drugs which generally allow better minute-to-minute control of the depth of anesthesia during longer interventions (see below).

Drug redistribution determines duration of anesthesia. Rapid entry of an agent into brain (a high blood flow organ) causes rapid induction of general anesthesia. However, subsequent **redistribution of the agent out of brain** to lower blood flow organs (muscle and fat), rather than drug metabolism or excretion, causes initial recovery of consciousness (see below). If

peripheral tissues become drug saturated, anesthesia becomes very prolonged and recovery now depends on metabolism and excretion to remove drug from brain before consciousness returns!

Continuous infusion allows intravenous dosing to be regulated in response to vital signs. Programmable pumps allow continuous drug infusions to smoothly maintain general anesthesia with much less danger of drug overdose than the bolus methods. Just enough intravenous agent is continually infused to sustain unconsciousness by replacing drug that is redistributing out of brain to other compartments.



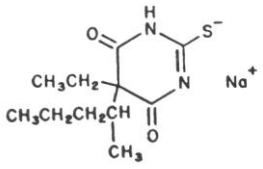
(LEFT) 1st bolus injection induces unconsciousness within seconds (above dashed line), but by 15 min plasma / brain drug levels fall below those sustaining anesthesia (sleep). **(RIGHT)** Initial rapid distribution to brain reverses as drug leaves brain for low blood flow tissues like muscle / fat. **(LEFT)** Repeated bolus injections cause longer "sleep" because redistribution from brain is slowed as drug uptake by muscle / fat drops as these compartments saturate. Brain levels remain elevated and anesthesia is sustained until much slower metabolism / excretion clears the drug.

Commonly used Intravenous Drugs

Ultra-Short Acting Barbiturates such as **thiopental** (Pentothal®) and **methohexital** (Brevital®) induce "complete general anesthesia" within as little as 10-20 seconds, but with small margin of safety. **There are no antagonists!** These agents can depress respiration and cardiovascular system with lethal results.

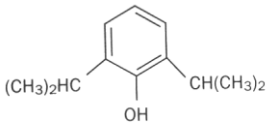
Barbiturates act at a unique binding site to allosterically increase affinity of $GABA_A$ receptors for GABA, ***but at higher concentrations also directly activate the GABA chloride channel independent of GABA*** [*see Frye, Anxiolytics, ... 10&11am 5/4/11*].

THIOPENTAL SODIUM
[Pentothal]



Propofol (Diprivan®) is a derivative of phenol capable of "complete general anesthesia". Actions are barbiturate-like, but is metabolized much more rapidly than barbiturates. **There are no antagonists!** Used for induction and continuous infusion anesthesia for shorter procedures with a greater degree of safety due to its faster clearance.

Propofol acts at a unique binding site to allosterically to increase the affinity of $GABA_A$ receptors for GABA, ***but at higher concentrations also directly activate the GABA chloride channel independent of GABA*** [think of propofol as "Barb-like", but with different binding sites [*see Frye, Anxiolytics, ... 10&11am 5/4/11*].

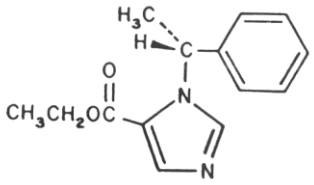


Propofol

Etomidate (Amidate®) is also similar to barbiturates with less severe cardiovascular and respiratory depressant effects and also rapidly hydrolyzed in the liver so clearance is faster than with barbiturates. **There are no antagonists!** Used for induction.

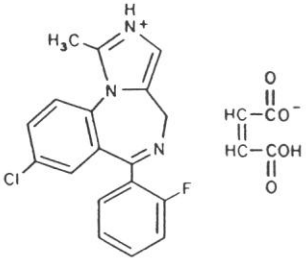
Etomidate acts at a unique binding site to allosterically to increase the affinity of $GABA_A$ receptors for GABA , ***but at higher concentrations also directly activate the GABA chloride channel independent of GABA*** [think of etomidate as "Barb-like", but with different binding sites [*see Frye, Anxiolytics, ... 10&11am 5/4/11*].

ETOMIDATE
[Amidate]



Benzodiazepines like **midazolam** (Versed®) and **diazepam** (Valium®) are **"incomplete general anesthetics"**, which can induce unconsciousness / amnesia in very large doses, but alone are not sufficient for major surgery -- but are useful in ***"balanced anesthesia"*** in combination with other depressants or alone for ***"conscious sedation"***. Both agents have active metabolites.

MIDAZOLAM HYDROCHLORIDE
[Versed]



Flumazenil (Romazicon®), is a competitive benzodiazepine antagonist (no intrinsic activity), that reverses the actions of midazolam and diazepam and can be used to reverse / offset benzodiazepine agonist-related CNS depression.

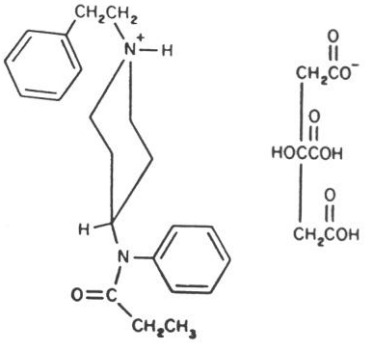
These agonist / antagonist actions are due to specific binding at unique "benzodiazepine receptor sites" on $GABA_A$ receptors. Agonists allosterically increase the affinity of the $GABA_A$ receptor for GABA, while a competitive antagonist prevents interaction of agonists with the binding site [*see Frye, Anxiolytics, ... 10&11am 5/4/11*].

Opioids such as fentanyl (Sublimaze®), alfentanil (Alfenta®) and sufentanil (Sufenta® / Remifentanil) are "complete general anesthetics" that cause profound analgesia, but also can severely depress respiration so are most often used in "balanced anesthesia".

Naloxone (Narcan®) is a competitive antagonist (no intrinsic activity) that reverses all CNS depressant actions of opioids including anesthesia.

Opioids act as agonists primarily on Mu opioid receptors to produce anesthesia and marked analgesia [*see Winzer-Serhan, Opioid Drugs, 11am 3/23/11*].

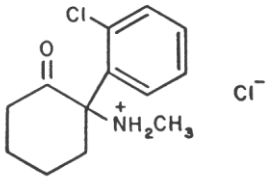
FENTANYL CITRATE
[Sublimaze]



Dissociative Anesthesia and Anesthetics

Ketamine (Ketalar®) can be used intravenously or <u>intramuscularly</u> to induce "complete general anesthesia". This general anesthesia is termed "<u>dissociative</u>" because the patient initially feels consciously detached from the environment before becoming unconscious. The dissociative state is marked by sedation, amnesia, immobility and marked analgesia.

KETAMINE HYDROCHLORIDE
[Ketalar]

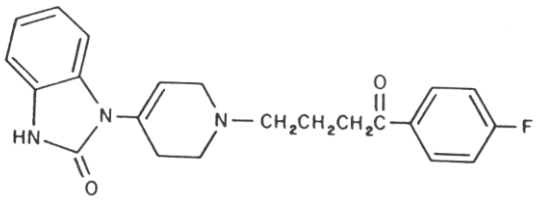


Ketamine is contraindicated in epileptic or psychiatric patients, since it can be associated with excitation / dysphoric hallucinations, particularly in adults, which may recur over days or weeks. It is also **contraindicated in hypertensives and cerebral vascular injury** since it increases cerebral blood flow and pressure.

Ketamine acts as a noncompetitive antagonist of N-methyl-D-aspartate (NMDA) type excitatory glutamate receptors.

Neuroleptanalgesia / Neuroleptanesthesia with **droperidol** and **fentanyl** in combination (Innovar®) are a neuroleptic or antipsychotic drug and intravenous opioid can <u>induce a dissociated state</u>. Complete anesthesia is not easily assured.

DROPERIDOL
[Inapsine]



Droperidol is an antagonist that blocks dopamine D_2 receptors and is **contraindicated in Parkinson's patients**.

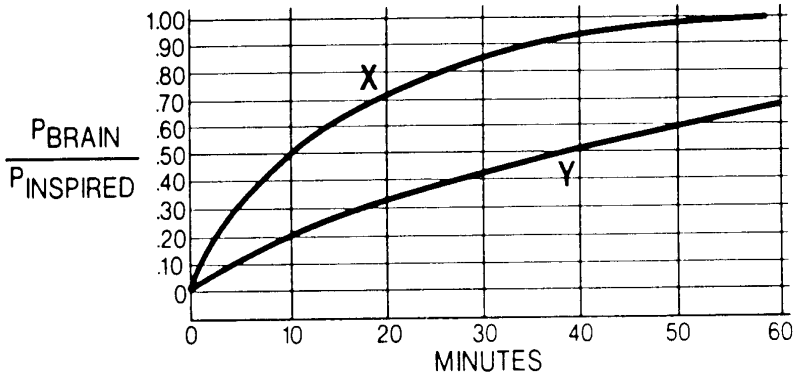
Fentanyl is an opioid acting on Mu receptors (see above). These agents can be supplemented with N_20.

SELF-STUDY QUESTIONS

Use the data in the following chart and table to answer the following THREE questions.

Anesthetic	Inspired Concen.*	Brain tension* causing anesthesia	Blood/gas partition (λ)
X	20%	380 mm Hg	0.1
Y	20%	76 mm Hg	10.0

* Atmospheric pressure = 760 mm Hg or 760 torr



Which is true for the drugs in the figure and table above?

a. Anesthetic X induces anesthesia within 30 minutes.
b. Anesthetic Y will not induce anesthesia when inhaled at this concentration.
c. Anesthetic X will induce anesthesia before Y.
d. Anesthetic Y is more blood soluble than X.
e. Anesthetic X is a more potent anesthetic than Y.

Which is true for the drugs in the figure and table above?

a. Y would be less likely to be metabolized than X.
b. inhaling 50% of X could cause equivalent CNS depression as inhaling 10% of Y.
c. inhaling 50% of X is more likely to cause respiratory arrest than inhaling 50% of Y.
d. inhaling CO_2 or manually increasing respiratory rate initially will not increase the rate of uptake of Y.
e. MAC for X is likely to be a smaller number than for Y.

If both drugs could continue to be inhaled until equilibrium, but are then removed from the gas mix:

a. X would be cleared by exhalation more slowly than Y.
b. The duration of post anesthesia hangover is likely to be the same with both X and Y.
c. The fraction of Y that would be exhaled unchanged would likely be larger than for X.
d. The metabolism of Y would likely be greater than X.
e. The partial pressure of X in brain would drop at a slower rate than that of Y.

Can reduce the depth of CNS depression during balanced general anesthesia that includes fentanyl?

a. xylidine
b. norepinephrine
c. naloxone
d. propofol
e. flumazenil

Rapid reversal of full general anesthesia after a single bolus injection of methobarbital:

a. occurs when methobarbital levels fall during redistribution from brain to fat and muscle.
b. depends on oxidation and conjugation of methobarbital to inactive products by hepatocytes.
c. requires complete loss of methobarbital from the brain.
d. involves rapid hydrolysis of methobarbital in the circulation by pseudocholinesterase.
e. can be achieved by competitive antagonism of Mu (μ) opioid receptors with flumazenil.

Inhalation anesthetic which is a halogenated ether and neither combustible nor explosive unlike diethyl ether?

a. nitrous oxide
b. ketamine
c. midazolam
d. isoflurane
e. propofol

d, b, d, c, a, d

GENERAL ANESTHESIA

INHALATION / INTRAVENOUS DRUGS

1st General Anesthesia?

LEFT - Painting shows William Morton (on left) administering diethyl ether general anesthesia to patient Gilbert Abbott for Surgeon Dr. John Warren in 1846 in surgical theater of Mass. Gen., (later called "The Ether Dome"). RIGHT - 1847 daguerreotype image of a enactment with Morton and Warren.

Painting by Robert Hinckley - hangs in Mass. Gen. Hospital Library

Taken by Albert S. Sands Southworth and Josiah Johnson Hawes - hangs in Getty Museum Los Angeles

Gerry Frye, 371 Reynolds
gdfrye@medicine.tamhsc.edu

OBJECTIVES

Introduce clinical utility of general / balanced anesthesia

Overview mechanisms of general anesthesia at systems and cellular level

Introduce drug classes combined to achieve balanced general anesthesia

Define inhalation anesthetic potency based on minimum alveoloar concentration (MAC)

OBJECTIVES (cont.)

Consider pharmacokinetic principles of inhalation anesthesia induction, maintenance & recovery

Discuss significant side effects / adverse events possible with inhaled agents

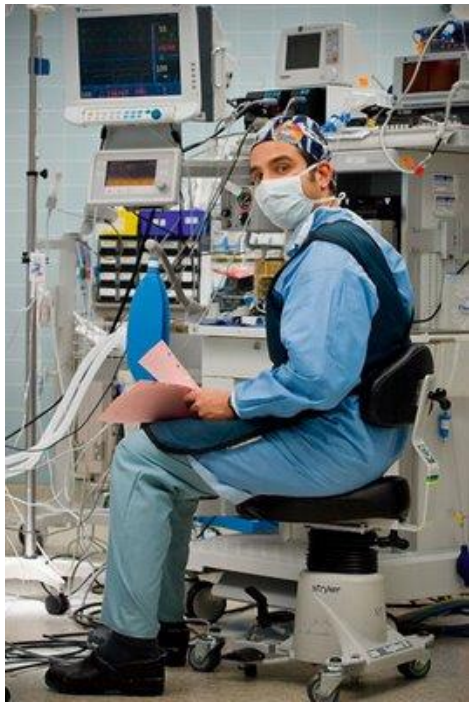
Understand pharmacokinetic influences on action of intravenous general anesthetics

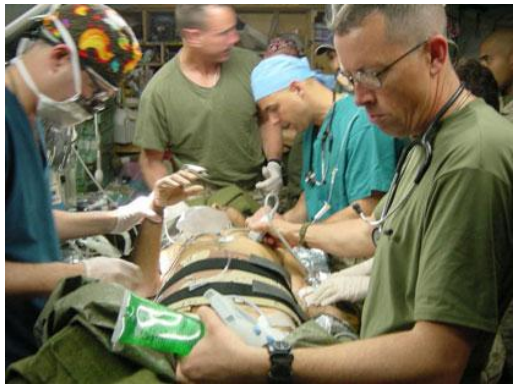
Define intravenous general anesthetic drug classes and prototypical agents

General or Balanced Anesthesia

Fully Reversible

Drug(s)-Induced State

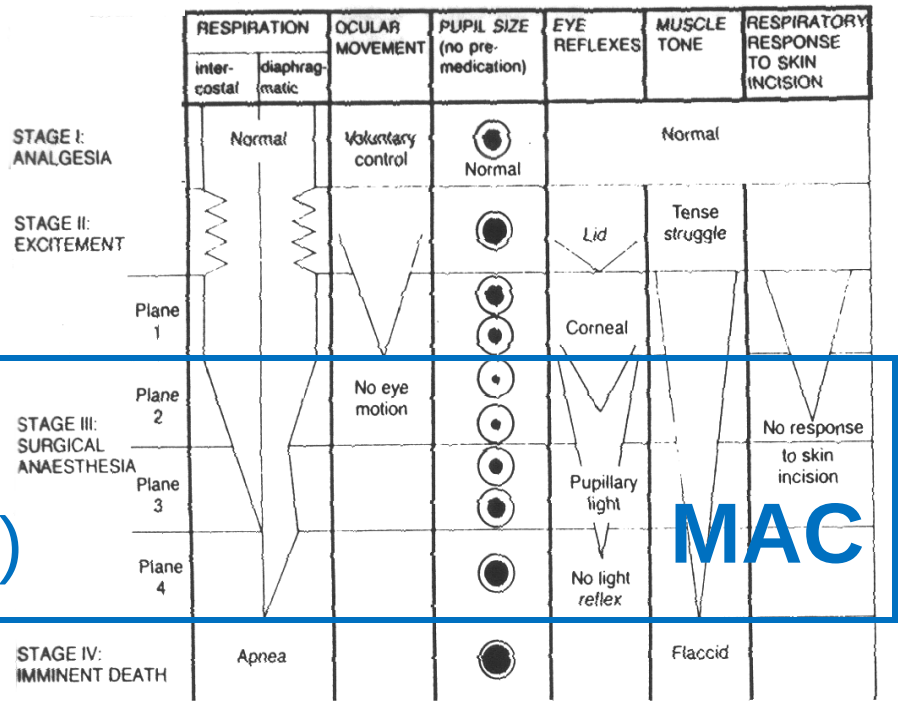




Complete loss of consciousness, awareness of pain and immediate memory

Clinical Signs of Diethyl Ether Anesthesia

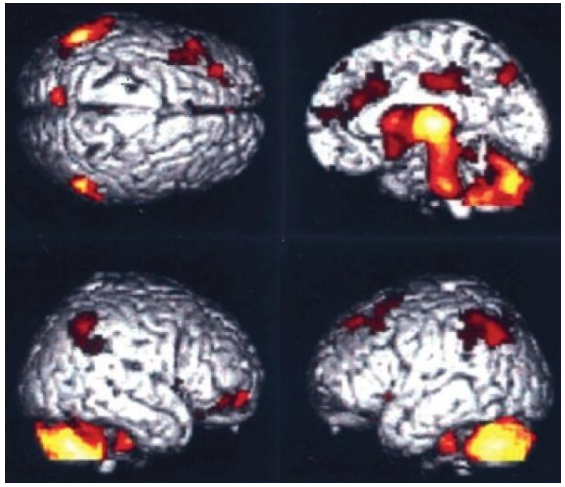
- I Stage of Analgesia
- II Stage of Excitation
- III Stage of Surgical Anesthesia (planes 1-4)
- IV Stage of Medullary Depression



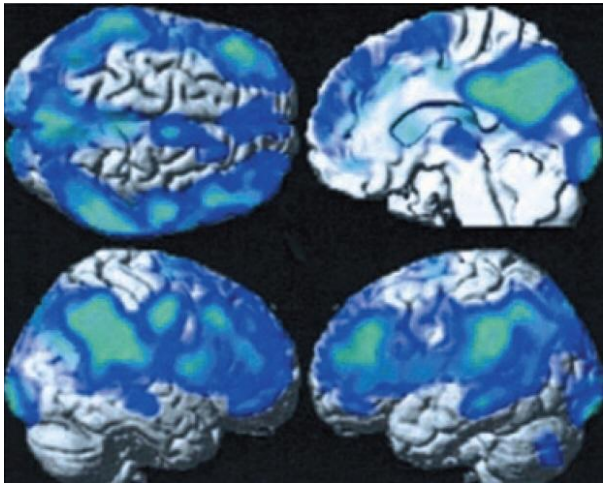
Modern drugs / equipment modify these signs

Loss of Consciousness / General Anesthesia occurs in CNS!

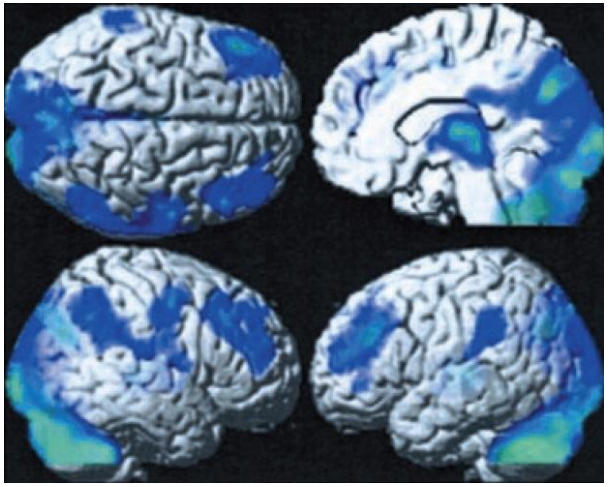
Non-REM Sleep



Propofol-Unconscious



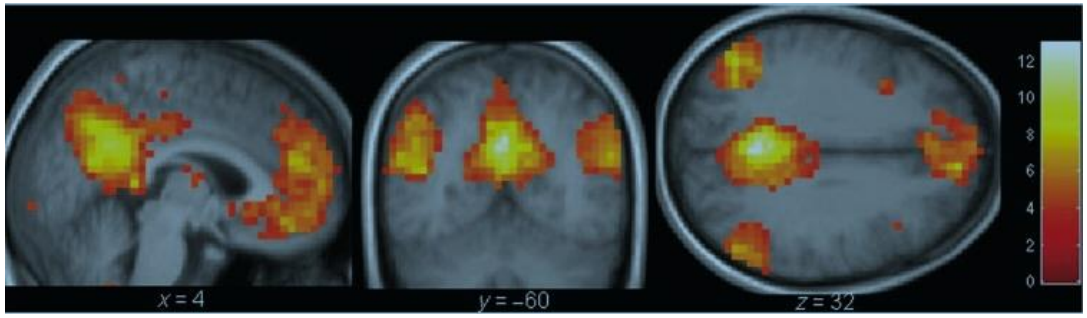
Sevoflurane-Unconscious



Franks, Nature Rev. Neurosci. 9:370-386, 2008

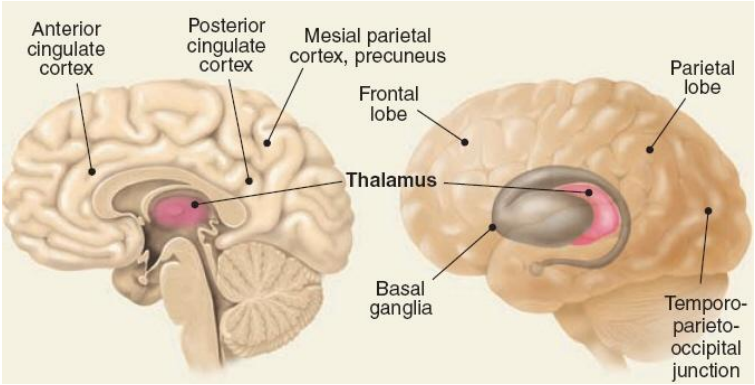
Changes in brain blood flow patterns during depressant general anesthesia are not uniform across the brain. Various cerebral cortical areas show reduced blood flow at lower anesthetic levels while loss of consciousness invariably involves reduced activity in thalamus, basal ganglia and brainstem. Similar changes have been noted in deep stage Non-REM sleep (a stage where someone is very difficult to awaken) and in the awake but unengaged / daydreaming brain (e.g. default brain network).

Default Brain Network in Daydreaming / Imagination



Vanhaudenhuyse et al., Brain 133:161-171, 2010

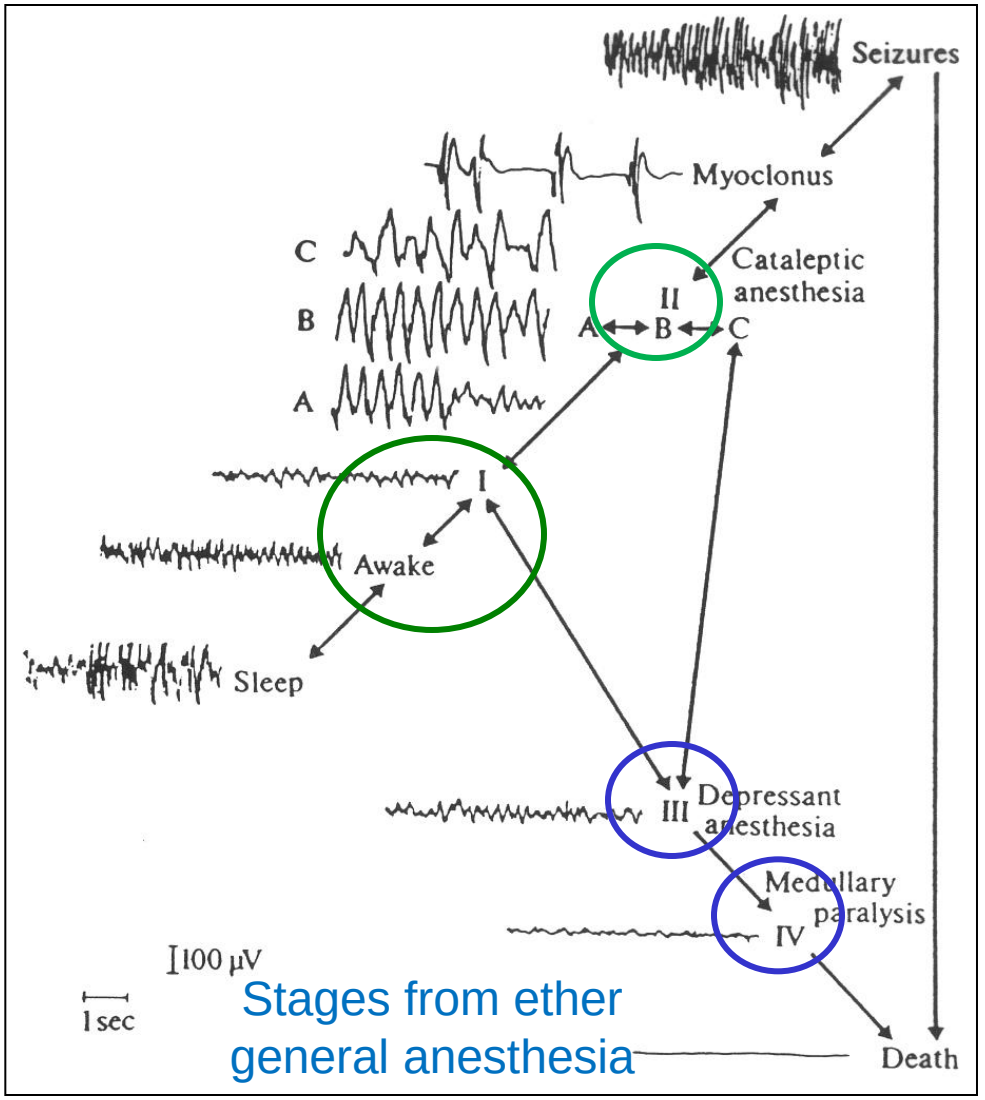
Brain areas where activity is altered in anesthesia



Alkire et al., Science 322:876-880, 2008

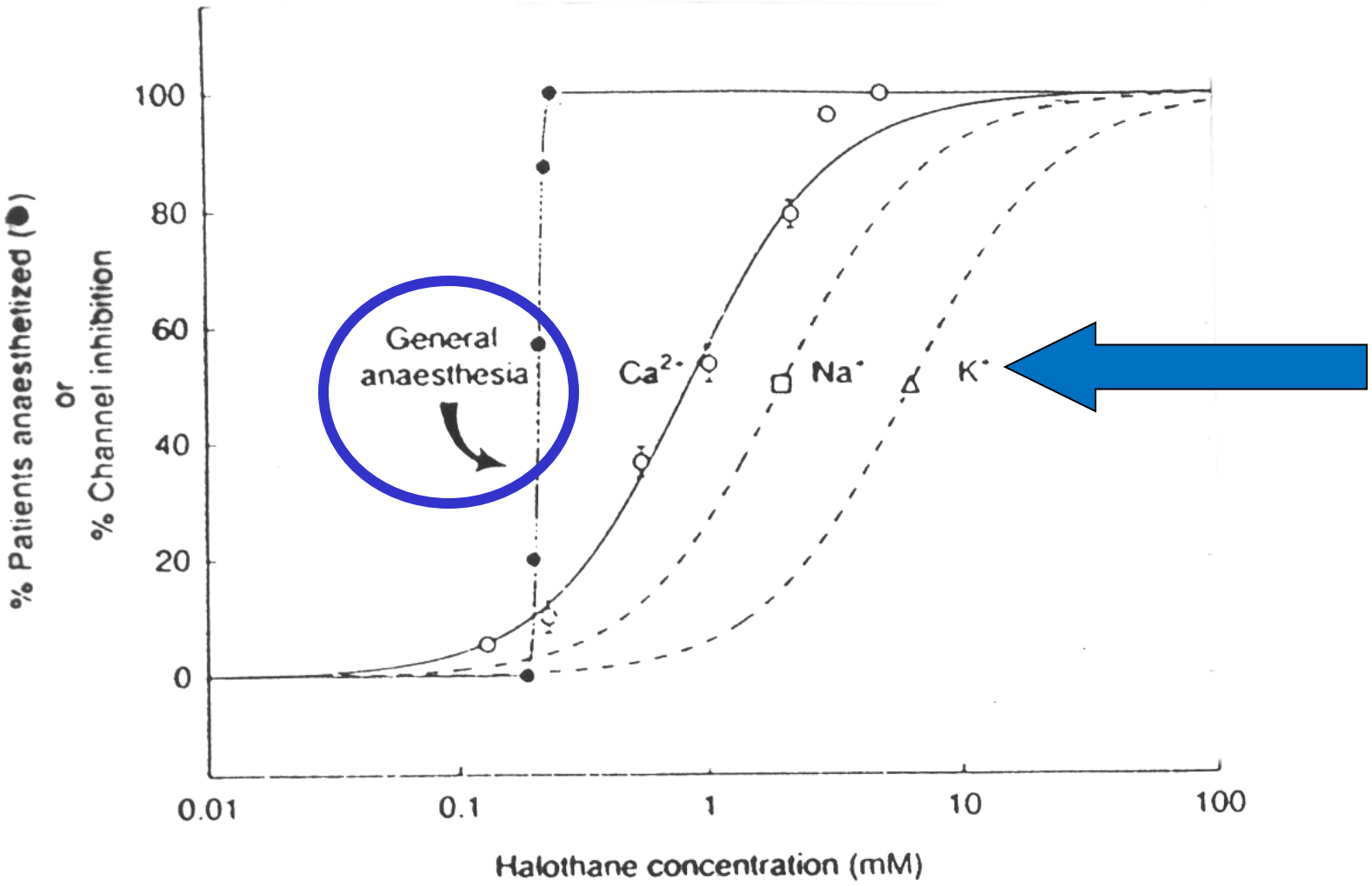
General Anesthesia occurs in CNS!

- Cerebral cortex - perception
- Reticulothalamic - alertness system
- Depressant General Anesthesia
- Dissociative General Anesthesia



Stages from ether general anesthesia

Cellular Sites of General Anesthetic Action



Molecular Sites of General Anesthetic Actions

Most Likely Target is

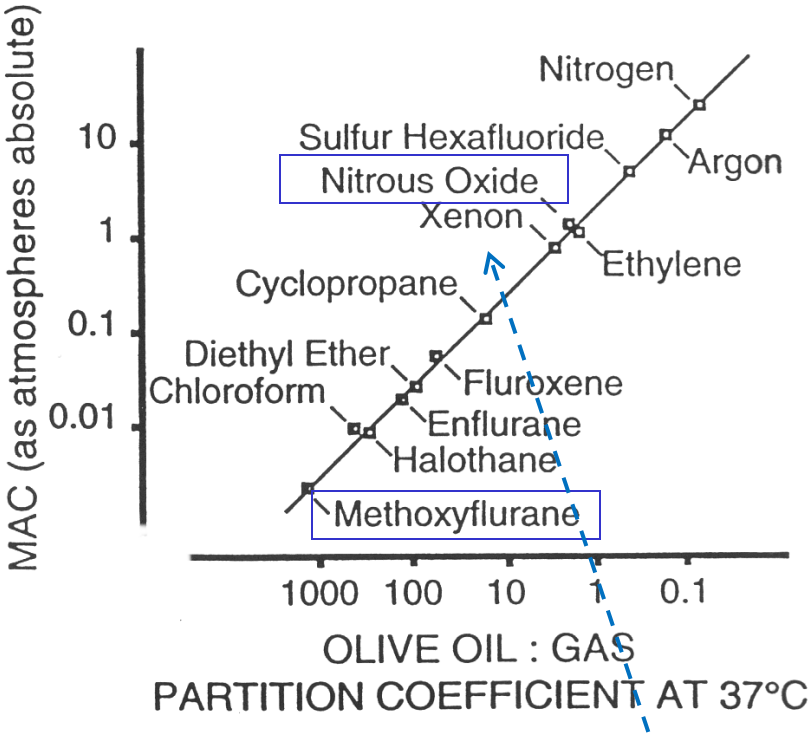
Neurochemical Synaptic Transmission at Specific Neurotransmitter Receptors

Ligand-gated ion channels - - GABA / glutamate receptors

G protein-couple ion channels - - opioid peptide receptors

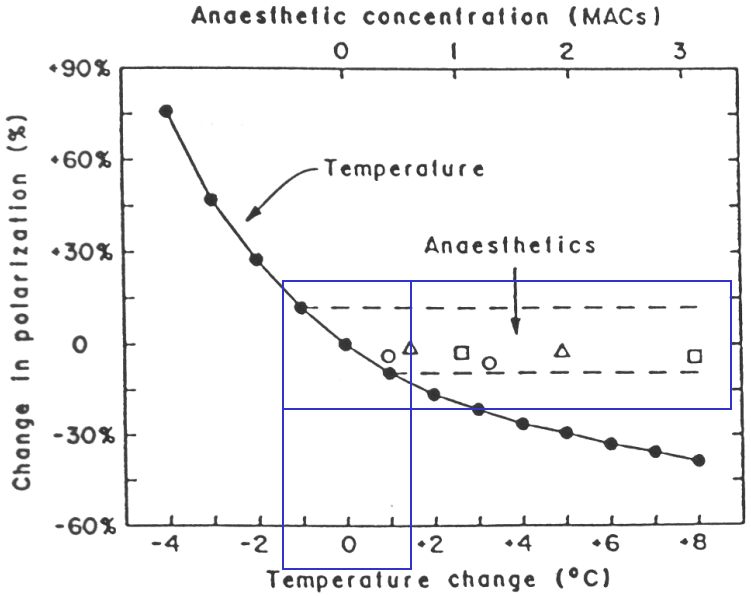
Two major theories of drug action!

Membrane Hypothesis

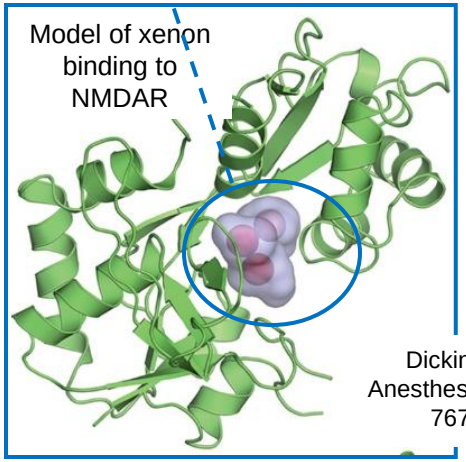


1905 Meyer-Overton - lipid solubility-potency correlation

1970s Seeman - membrane expansion-fluidization concept



Membrane hypothesis has lost much support!



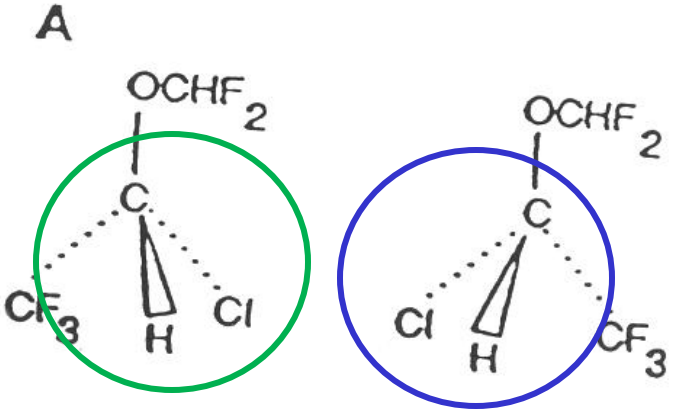
Dickinson et al Anesthesiol. 107:756-767, 2007

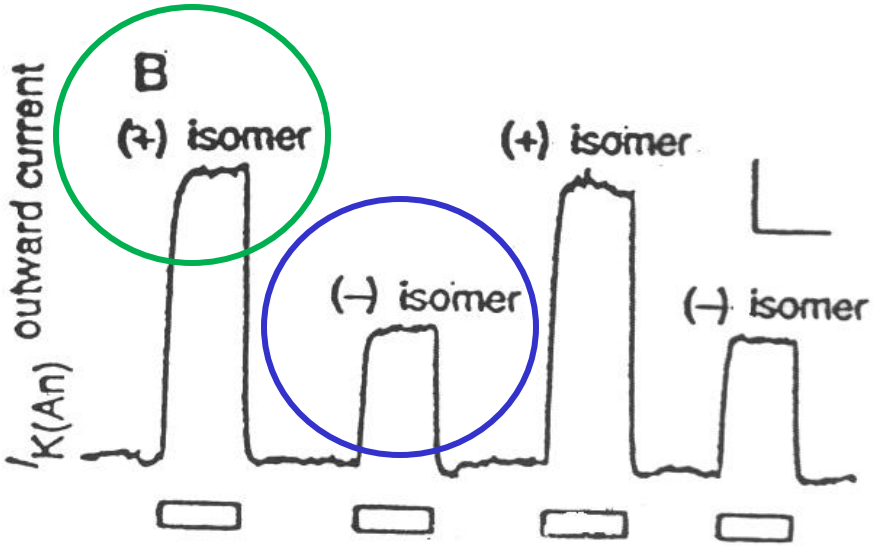
Protein Hypothesis

Binding directly to hydrophobic pockets

Specific interaction with receptor targets

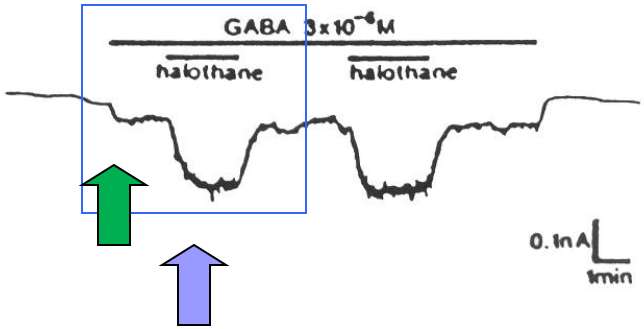
Isoflurane isomers

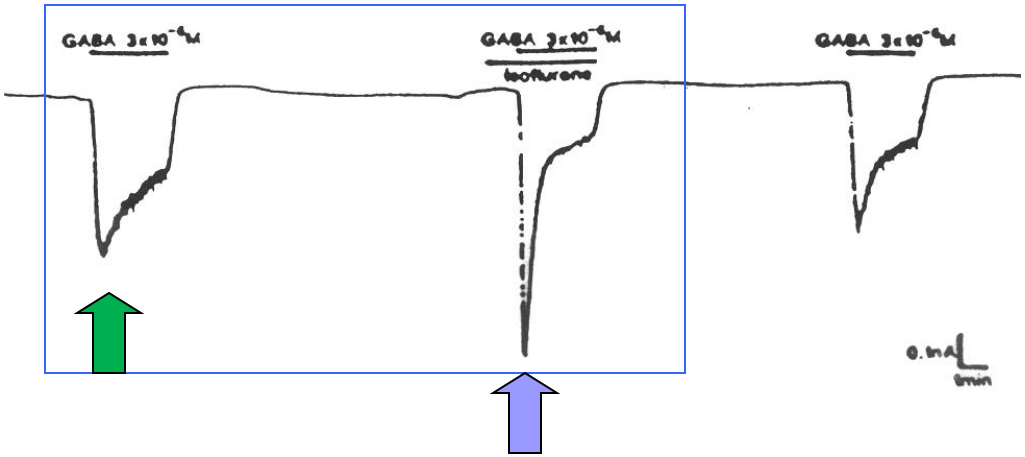




Specific Receptor Targets

- **$GABA_A$ Receptors** - Barbs, BZs, Propofol, Etomidate and Inhalation Anesthetics

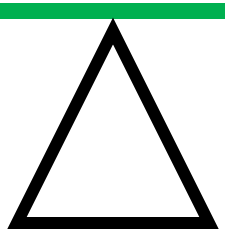




- **NMDA Glutamate Receptors** - Ketamine
- **Mu Opioid Receptors** - Fentanyl, Morphine

General Anesthesia

Balanced



- Uses both inhalation & intravenous drugs
- Combination of drugs maximizes benefits
- Reduces individual drug doses
- Safer / better tolerated than single agents
- Less adverse psych. / physiol. reactions

Modern Inhalation Anesthetics

Halogenated hydrocarbons / ethers

Desflurane CF_3-CHF-O-CF_2H Isoflurane CF_3CHCl-O-CHF_2

Halothane CF_3-CHClBr Enflurane CHF_2-O-F_2CHFCl

Sevoflurane CH_2F-O-$CH(CF_3)_2$

Non-irritating to breath
(except desflurane)

Non-explosive / non-combustible

Combined with air / O_2 / nitrous oxide

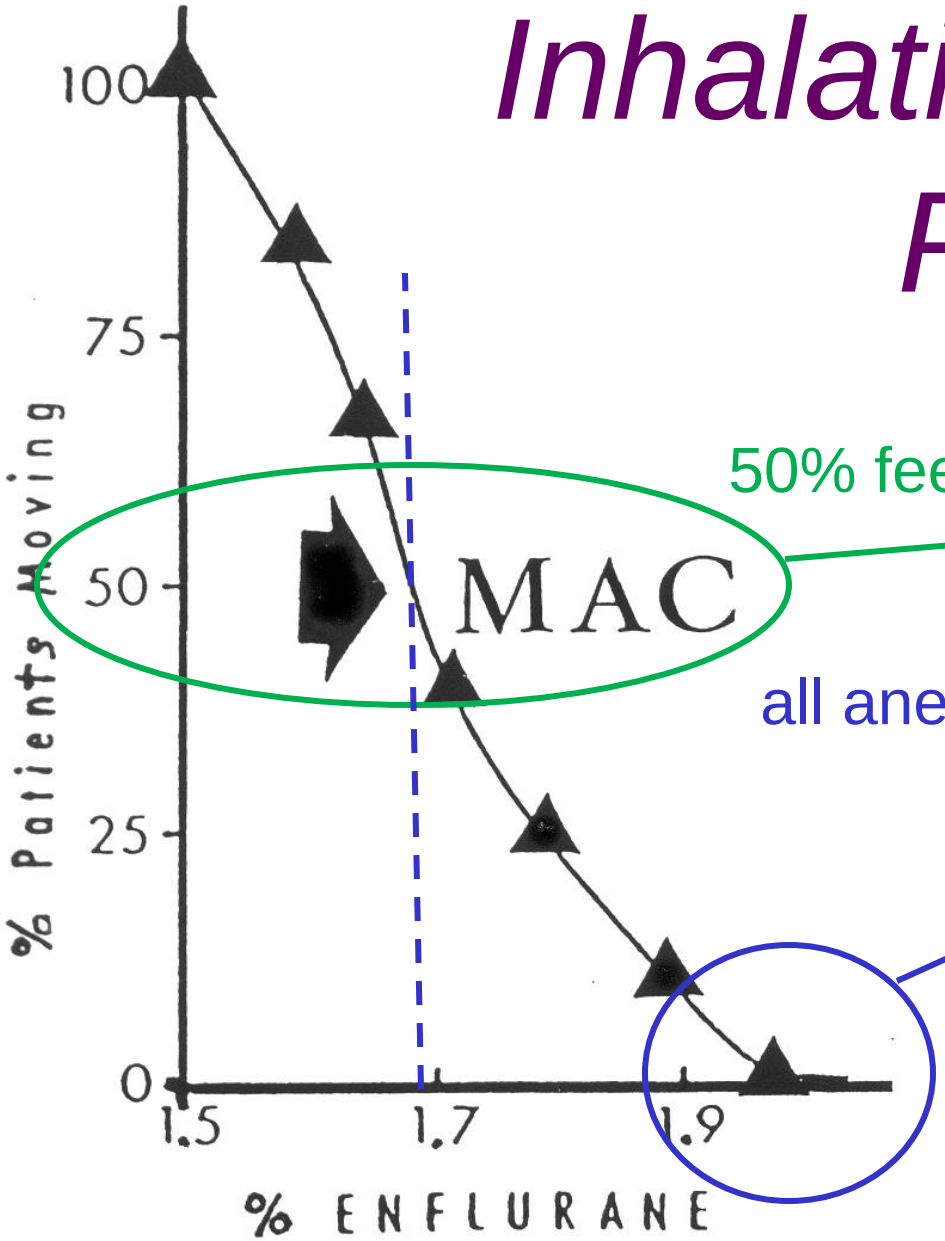
Nitrous Oxide N_2O

Other Drugs in Balanced Anesthesia

Preanesthetic / Supplements / Intravenous Agents

- Benzodiazepines - anxiolytic, amnesic, induction
- Short-acting barbiturates - induction
- Opioids - analgesia, induction & maintenance
- D_2 or $5HT_3$ blockers - nausea
- Antimuscarinics - secretions, bradycardia, nausea
- Proton pump or H_2 blockers / antacids, etc. - gastric acid aspiration
- Depolarizing anti-nicotinic - skeletal muscle tone
- Nitrous oxide - analgesia & partial general anesthesia

Inhalation Anesthetic Potency



50% feel no pain - like an ED_{50}

all anesthetized @ ~ 1.3X MAC

MAC a is unique % of gas for each drug!

Other depressants reduce MAC requirements

***Minimum Alveolar Concentration* = MAC**

Modern Drug *MAC* Values

	MAC (%)		
Methoxyflurane	**0.2**	**> > > > > >**	**Most potent**
Halothane	0.8		
Isoflurane	1.4		
Enflurane	1.7		
Sevoflurane	2.0		
Desflurane	6.5		
Nitrous oxide	**>100**	**> > > > > >**	**Least potent**

MAC values are helpful in estimating initial dose targets

MAC is Resistant to Change

With These Exceptions

- Age decreases MAC

- Changes in body temp. inversely alters MAC value

- Combinations of inhalation drugs have additive CNS effects

(ie., 1/2 MAC + 1/2 MAC = 1 MAC)

- Stimulants increase but depressants decrease MAC

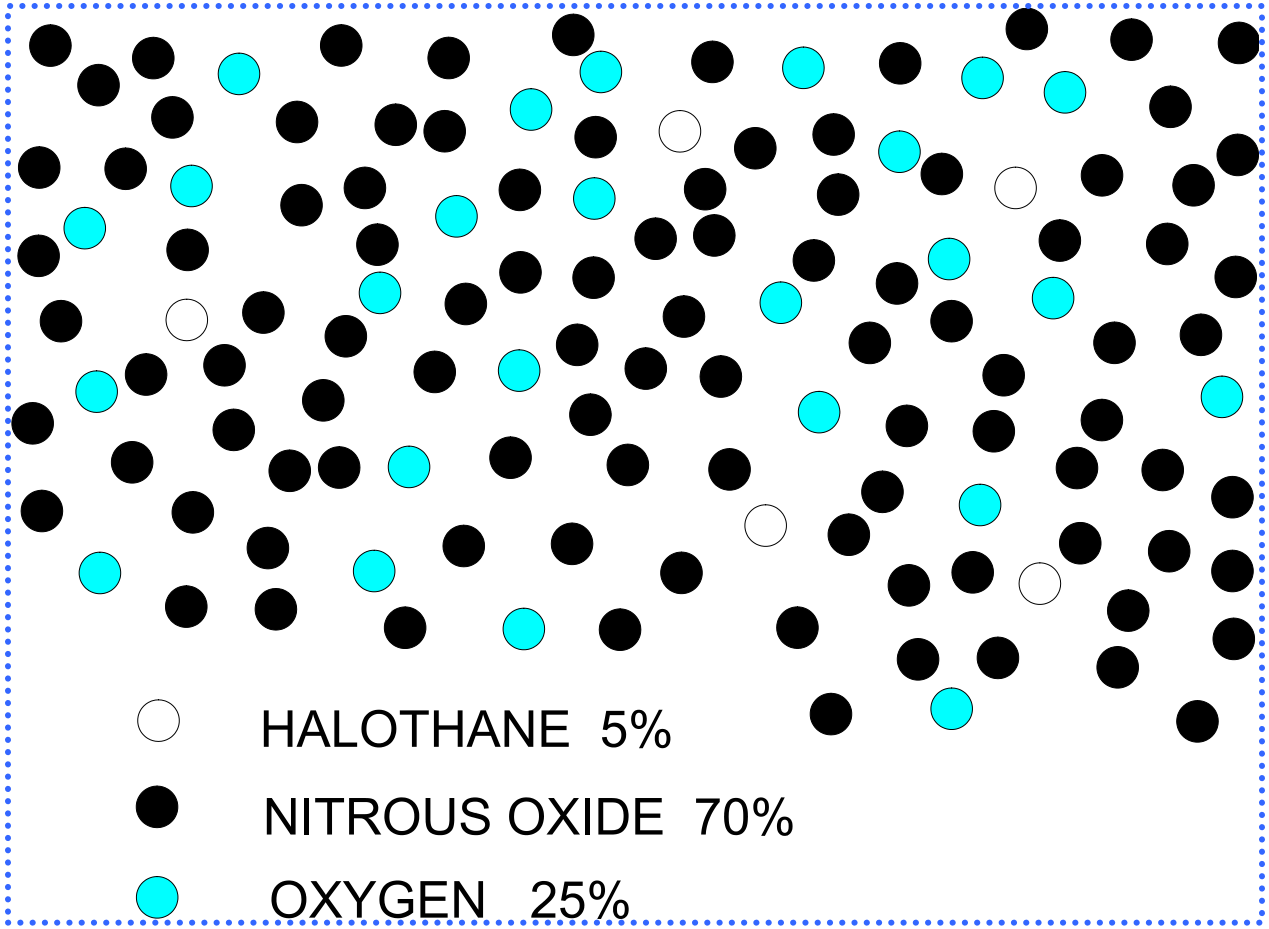
- Cross tolerance with CNS depressants increases MAC value

GAS Concentrations @ 1 atmosphere

Air = 21% O_2 + 79% N_2

Air = 160 mmHg O_2 + 600 mmHg N_2

Air = 160 torr O_2 + 600 torr N_2

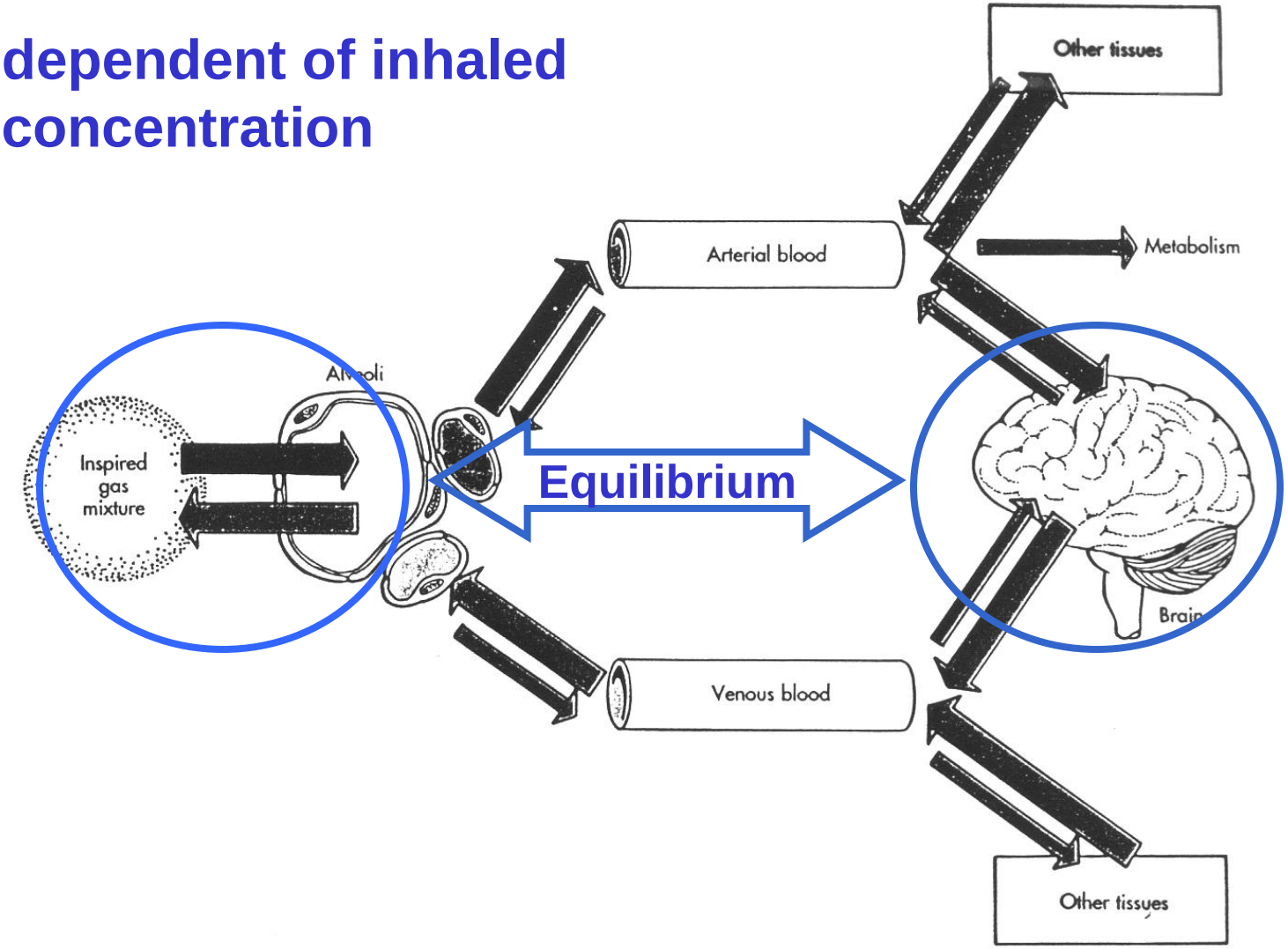


concentration (%) = partial pressure (mmHg) = tension (torr)

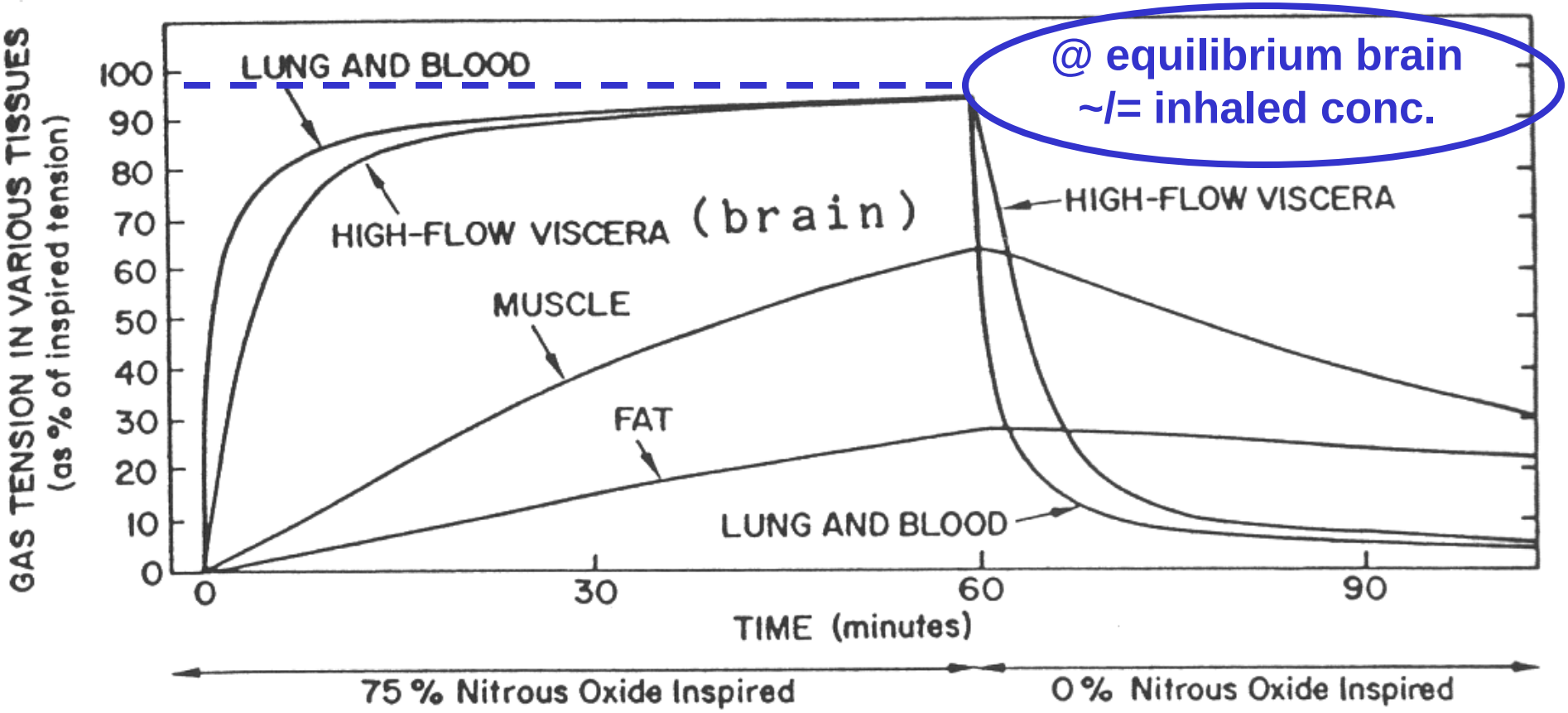
1 atmosphere = 100% = 760 mmHg = 760 torr

Inhalation Anesthetic Pharmacokinetics

MAC independent of inhaled concentration



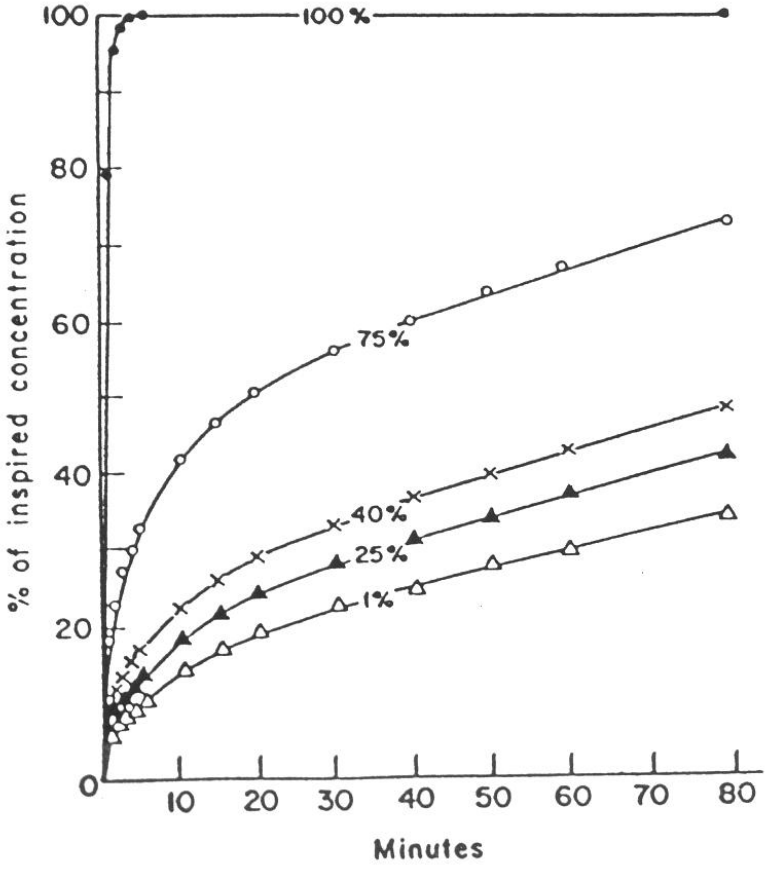
Anesthesia depends on brain tension!

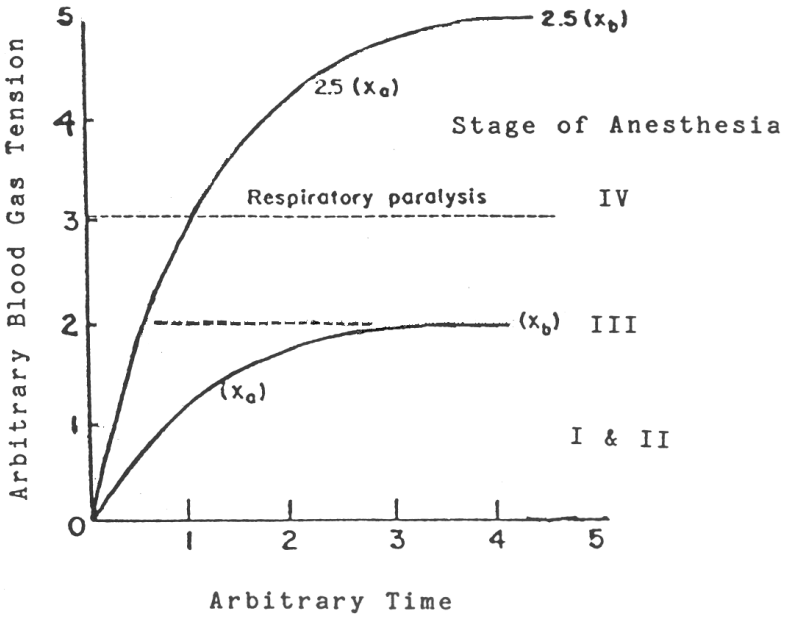


Tissue tensions of an anesthetic gas during uptake and elimination.

Increasing respiration rate speeds induction temporarily - but no effect on final brain tension or MAC value!

High blood flow organs get drug fastest (induction) and also loose it fastest (recovery)!





Inhaling higher anesthetic concentrations speed uptake!

Equilibrium = total brain & body saturation

Recovery depends on how fast drug leaves brain!

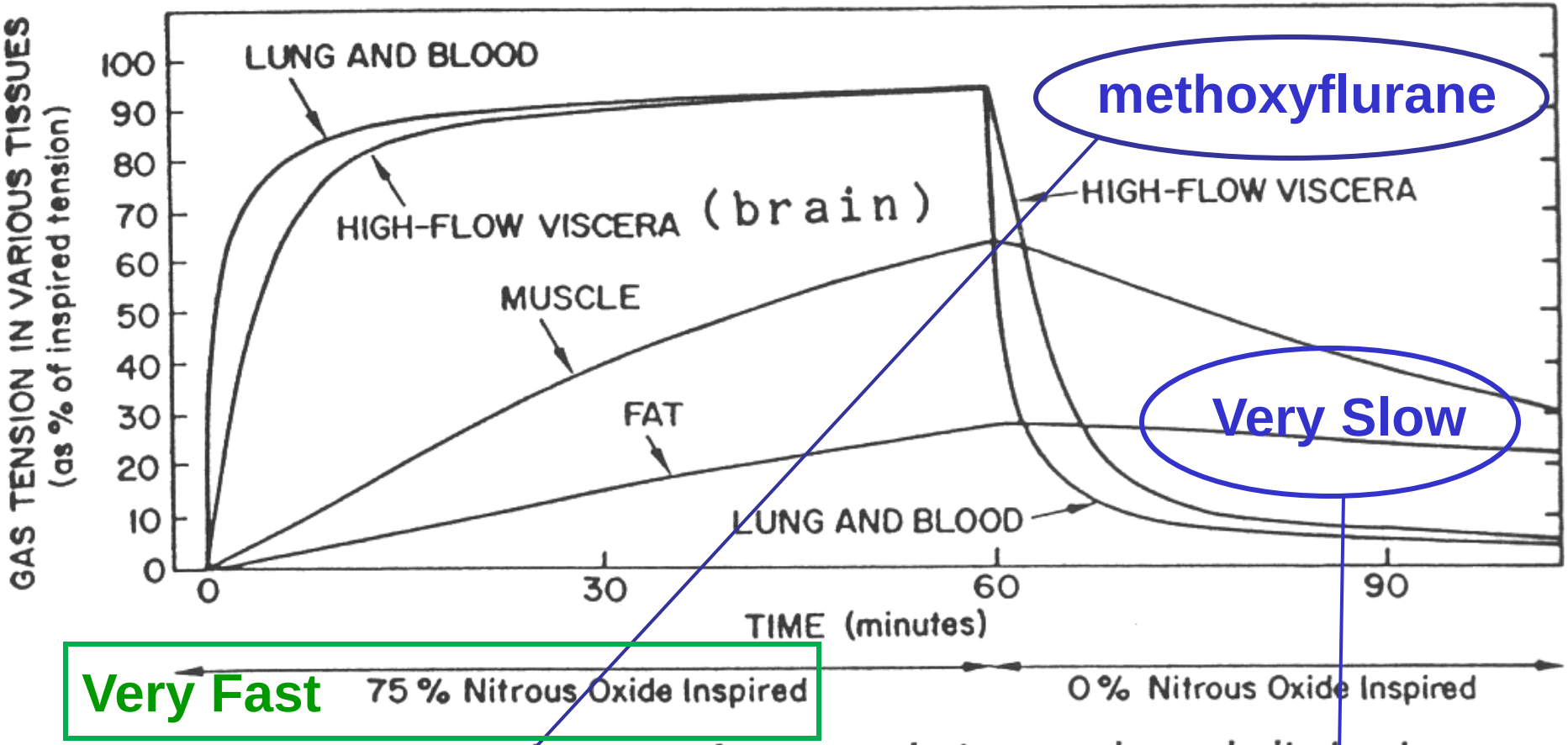
Blood : Gas Values for Modern Inhalation Agents

Blood:Gas Partition Coefficients (λ)

Desflurane	**0.42**	**> > > >**	**Least blood soluble**
Nitrous oxide	0.47		
Sevoflurane	0.69		
Isoflurane	1.4		
Enflurane	1.8		
Halothane	2.3		
Methoxyflurane	12.0		
Diethylether	**12.1**	**> > > >**	**Most blood soluble**

Small λ = low solubility (affinity) - rapid access to brain

Large λ = high solubility (affinity) - slows access to brain



Tissue tensions of an anesthetic gas during uptake and elimination.

methoxyflurane

Very Slow

Very Fast

High blood solubility (affinity) slows rise in brain tension - prolongs induction - increases low blood flow tissue levels

High blood solubility (affinity) slows fall of brain tension - prolongs recovery - increases opportunity for metabolism

Other Drug Actions of Clinical Concern!

Respiratory Depression

CO_2

Anesthesia Hangover
metabolites / withdrawal?

Impaired CV Function

< Cardiac Contractions

Depress SA Node

Ca^{2+}

Atropine - Bradycardia

Halothane Sensitizes Heart

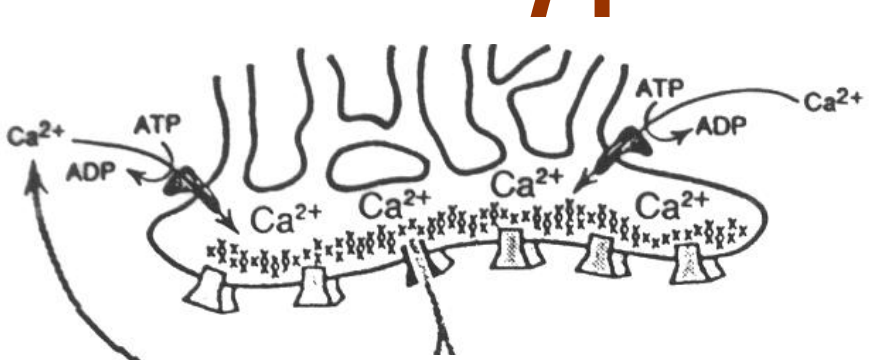
Reduce Blood Pressure

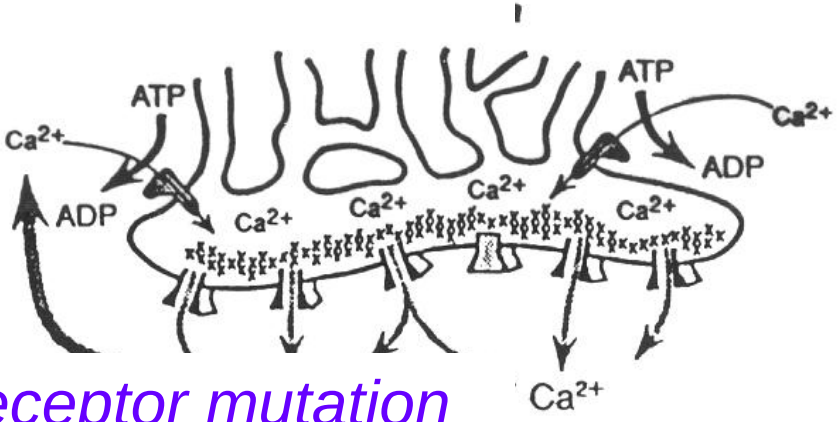
Adrenergics Increase BP

Succinylcholine interactions

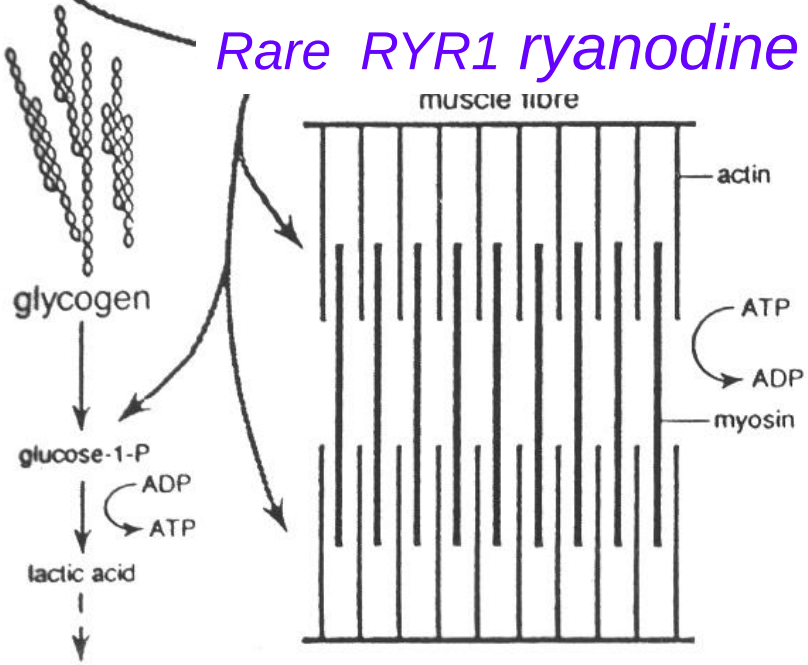
- Increase Intraocular Pressure
- Hyperkalemia
- Muscle Pain
- Increase Intragastric Pressure

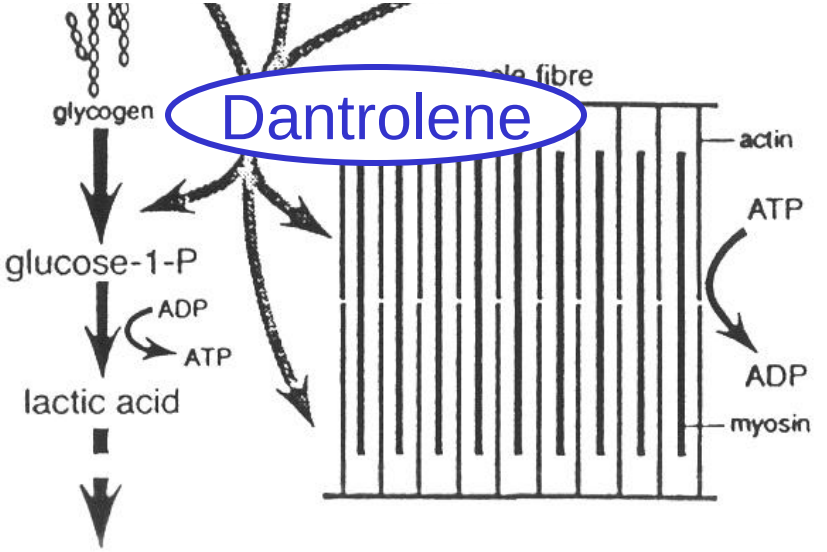
Malignant Hyperthermia





Rare RYR1 ryanodine receptor mutation





Exhalation - Primary Route of Elimination

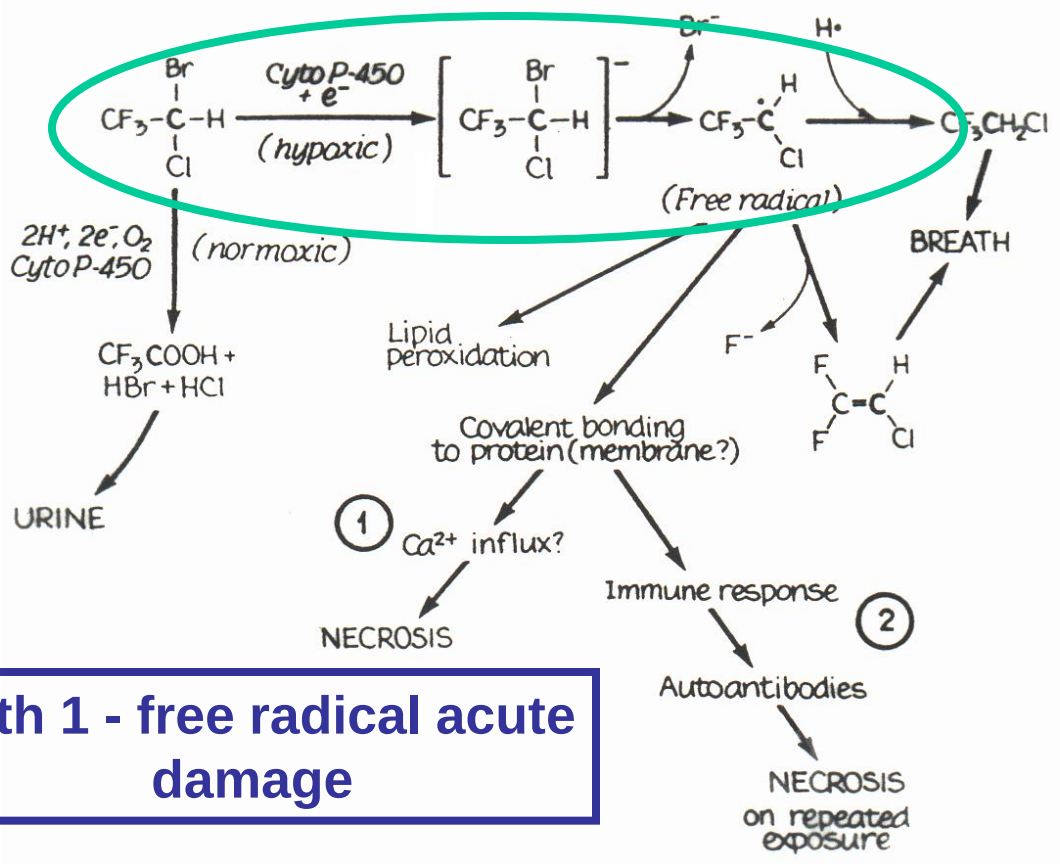
Agent	Excreted unchanged	Blood Solubility
methoxyflurane	**40%**	**12.0**
halothane	80%	2.3
enflurane	90%	1.8
sevoflurane	97%	0.69
isoflurane	98%	1.4
nitrous oxide	> 99%	0.47
desflurane	> 99%	0.42

Methoxyflurane 60% metabolized > 40μM F^- = Nephrotoxic

Halothane Hepatitis

Relatively Rare!

Life-threatening viral-like liver damage

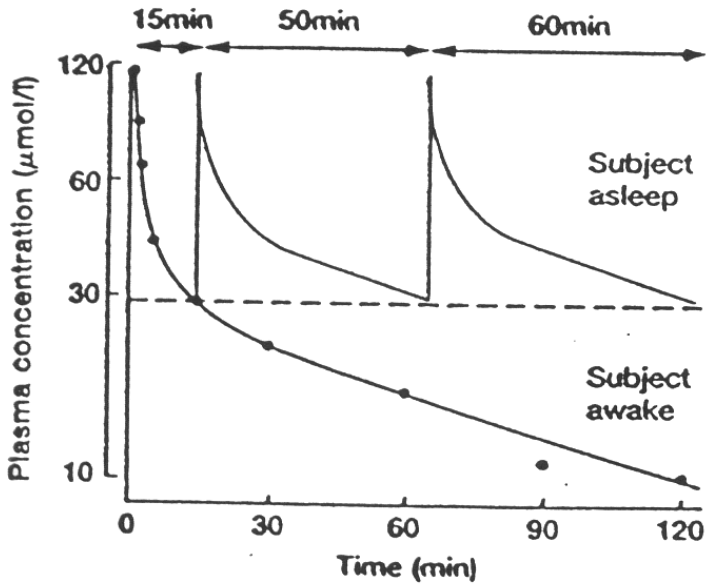


Path 1 - free radical acute damage

Path 2 - free radical adduct autoimmune damage

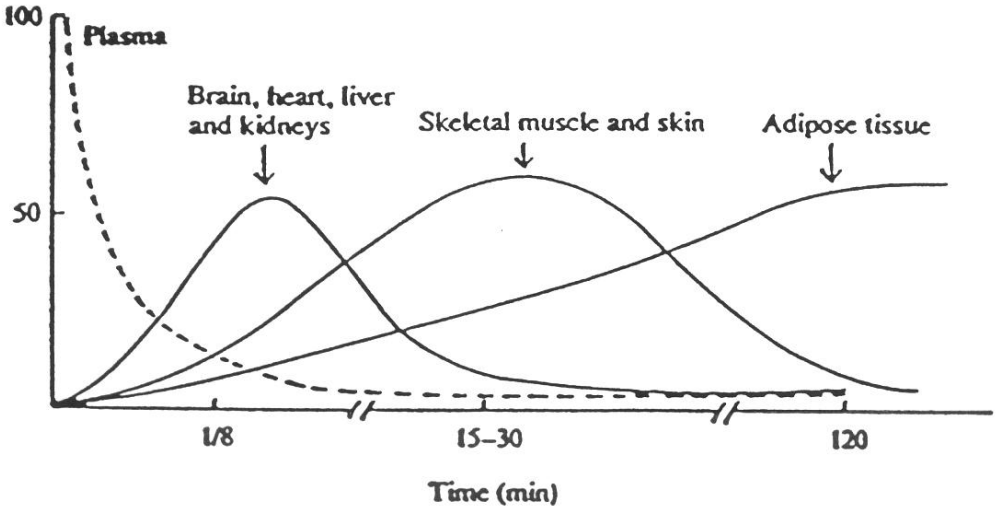
1st or 2nd exposures can trigger

Induction / Maintenance of General Anesthesia with Intravenous Drugs

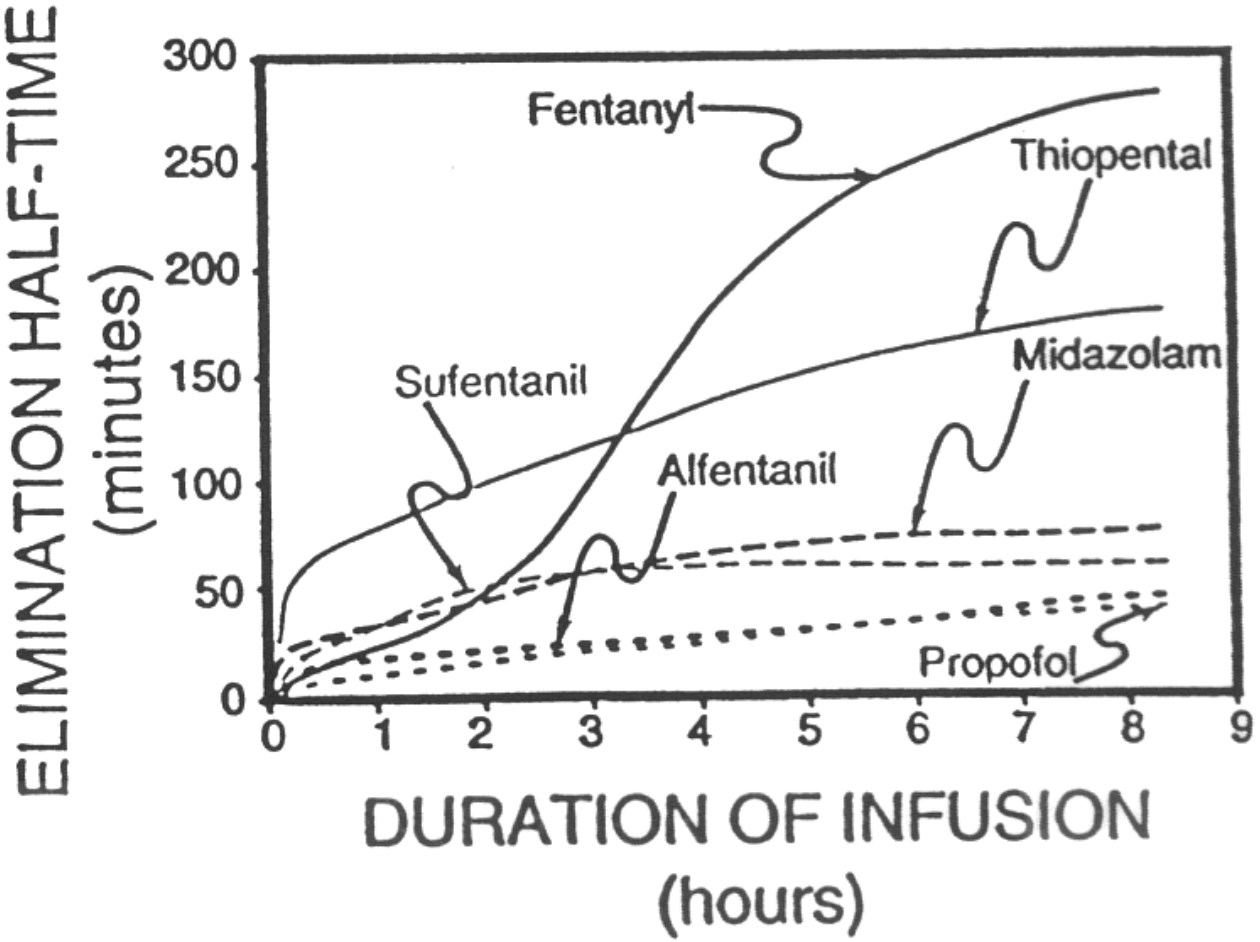


I.V. bolus vs infusion

Redistribution vs metabolism

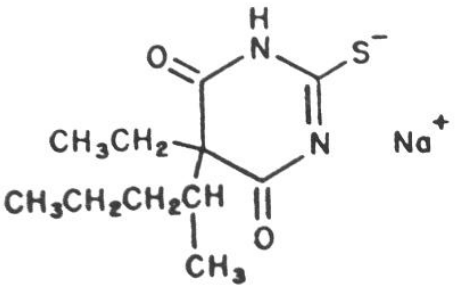


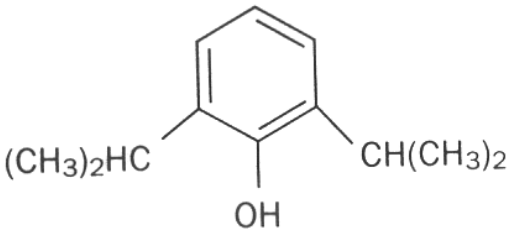
General Anesthesia by Continuous Infusion



Ultra-Short Acting Barbiturates / Related Drugs

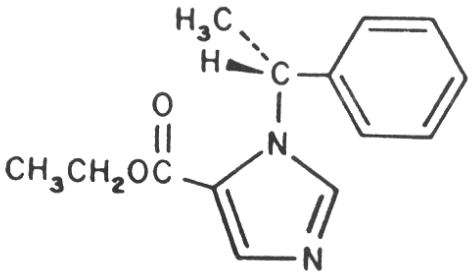
THIOPENTAL SODIUM
[Pentothal]





Propofol

ETOMIDATE
[Amidate]

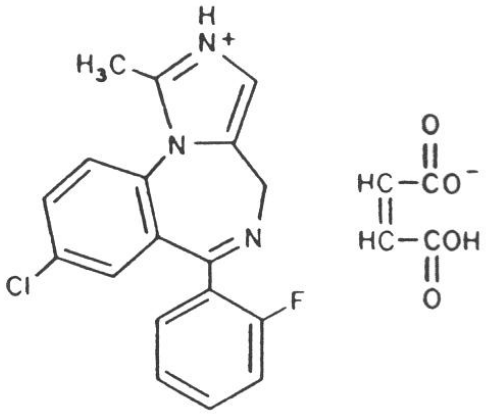


Benzodiazepines

GABA$_A$ Receptors

flumazenil

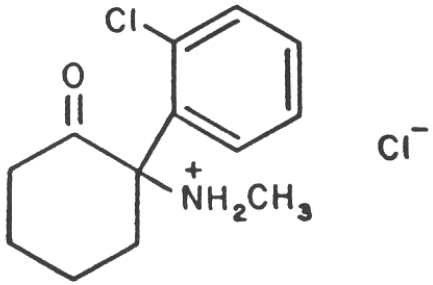
MIDAZOLAM HYDROCHLORIDE
[Versed]



Dissociative Intravenous Anesthetics

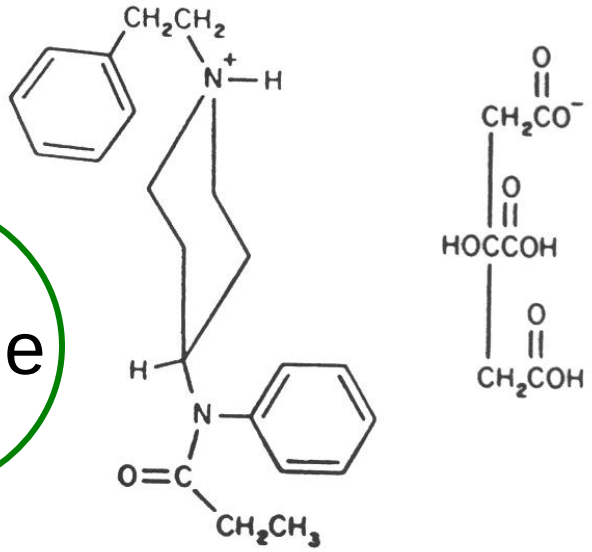
NMDA glutamate Receptors

KETAMINE HYDROCHLORIDE
[Ketalar]



Mu Opioid Receptors

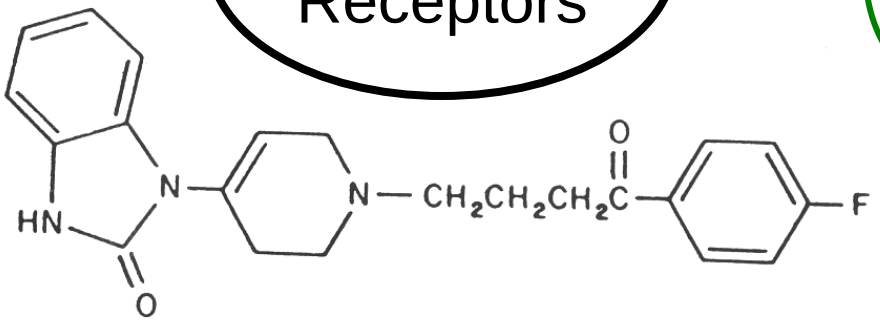
FENTANYL CITRATE
[Sublimaze]



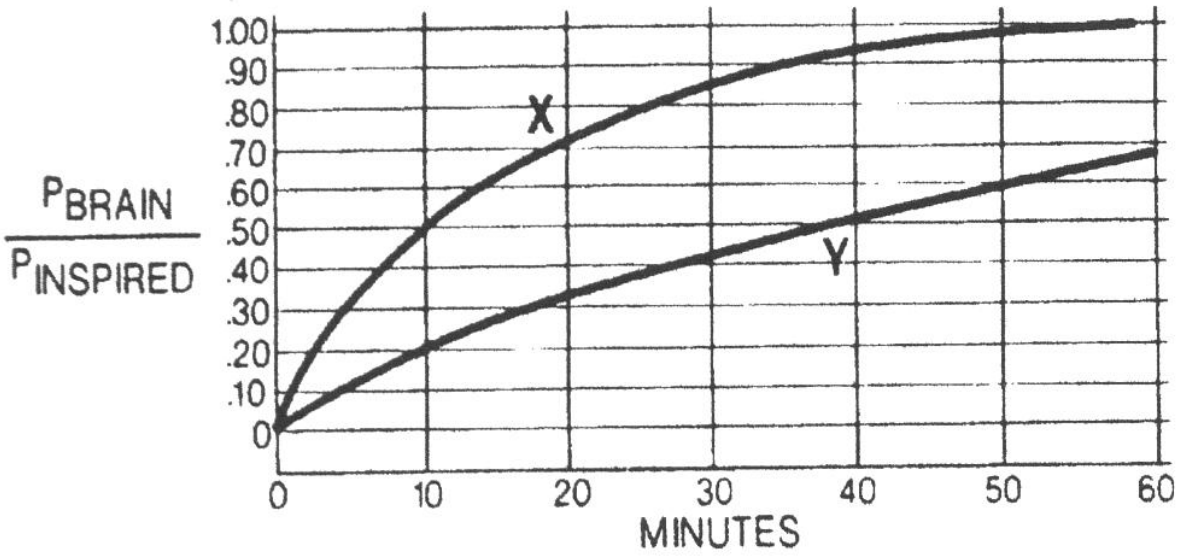
DROPERIDOL
[Inapsine]

Dopamine D_2 Receptors

naloxone



Self-Study Question -- Inhalation Anesthesia



Anesthetic	Inspired Concen.*	Brain tension* causing anesthesia	Blood/gas partition (λ)
X	20%	380 mm Hg	0.1
Y	20%	76 mm Hg	10.0

* Atmospheric pressure = 760 mm Hg or 760 torr